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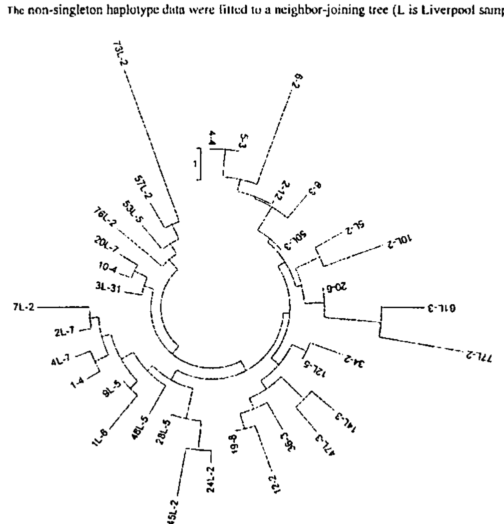
The non-singleton haplotype data were fitted to a neighbor-joining tree (L is Liverpool sample):



(57) Abstract: The present invention is based on sequencing genomic DNA from human chromosome 6 and cDNAs to define the genomic structure of estrogen receptor alpha genes and novel polymorphism/haplotypes in the estrogen receptor gene/protein. Such polymorphism/haplotypes can lead to a variety of disorders that are mediated/modulated by a variant estrogen receptor, such as a susceptibility to cancer, osteoporosis, cardiovascular disorder, etc. Based on this sequencing approach, the present invention provides genomic nucleotide sequences, cDNA sequences, amino acid sequences and sequence polymorphism/haplotypes in the ESR-alpha genes, methods of detecting these sequences/polymorphism/haplotypes in a sample, methods of determining a risk of having or developing a disorder mediated by a variant estrogen receptor and methods of screening for compounds used to treat disorders mediated by a variant estrogen receptor.

WO 01/62969 A2

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ESTROGEN RECEPTOR ALPHA VARIANTS AND METHODS OF DETECTION THEREOF

RELATED APPLICATIONS

The present application claims priority to applications U.S. Serial No. 60/183,756, filed February 22, 2000 (Atty. Docket CL000258-PROV); U.S. Serial No. 09/692,414, filed October 20, 2000 (Atty. Docket CL000258); and U.S. Serial No. 09/768,184, filed January 24, 2001 (Atty. Docket CL000258CIP).

FIELD OF THE INVENTION

The present invention is in the field of disease detection and therapy. The present invention specifically provides the identification of previously unknown nucleic acid/amino acid polymorphisms within the estrogen receptor alpha gene (ESR-alpha) and the genomic sequence of this gene for use in the development of diagnostics and therapies for diseases and disorders mediated/modulated by the estrogen receptor.

BACKGROUND OF THE INVENTION

Estrogen Receptor

The human estrogen receptor alpha belongs to the nuclear hormone receptor family. Nuclear hormone receptors are a family of hormone-activated transcription factors that can initiate or enhance the transcription of genes containing specific hormone response elements.

The ER protein consists of 595 amino acids with a molecular weight of 66 kDa, 8 transcribed exons, with six different functional domains. Two of those domains are highly conserved in the primary sequence of members of the nuclear hormone receptor superfamily. One of the domains, the DNA binding domain (DBD), contains two zinc fingers that mediate receptor binding to hormone response elements in the promoters of hormone-responsive genes. In the C- terminal region, the hormone-binding domain (HBD) contains two regions of sequence homology with other hormone receptors and gives hormone specificity and selectivity. The human ER-alpha gene is located in chromosome 6q.25.1.

Estrogen receptors, like other steroid receptors, are transcription factors that are activated upon binding to steroids (estradiol) or steroid analogs such as tamoxifen. Upon activation the receptors dimerize to form homodimers or heterodimers that bind to estrogen receptor elements (EREs) located in the promoter region of estrogen-activated genes and coordinate transcription by interacting with host co-activators.

Role of Estrogen in Cardiovascular Disease

Heart disease is the leading cause of mortality in women, a fact that is under appreciated by both women and physicians. One in 9 women aged 45-65 have some form of cardiovascular disease and the number increases to 1 in 3 after age 65. Each year, 240,000 U.S. women die from heart disease, and nearly 90,000 die of stroke. Moreover, approximately 44% die within one year of suffering a heart attack, compared with 26% of men (Warren MP and Kulak J Clin Obs Gyn 1998 41(4):976-987).

Estrogens exert a wide range of physiological effects on a large variety of cell types. For example, they regulate cell growth and apoptosis and a myriad of functions related to reproduction. There are two types of estrogen receptors, alpha and beta. Blood vessels and bone contain beta receptors, the liver has alpha receptors, and both alpha and beta receptors are found in the central nervous system. The interaction of these different receptor sites influences the biological effects of estrogen and selective estrogen receptor modulators (SERMs), such as raloxifene. The binding patterns dictate whether an estrogen or a SERM acts as an estrogen agonist or an antagonist (Mendelsohn ME and Karas RH New Engl J Med 1999, 340(23):1801-1811;Grese TA and Dodge JA Curr Pharm Design 1998, 4:71-92). Tissue-specific relationships exist between SERMs and the receptor binding sites. Estrogens also increase high-density lipoprotein cholesterol levels, decrease low-density lipoprotein cholesterol, and decrease plasminogen-activating inhibitor levels (Meisler JG Jour Women's Health 1999, 8(1):51-57). All estrogens require cellular receptors for their expression. In general, estrogen receptors are ligand-inducible transcription factors, which regulate the expression of target genes after hormone binding (Faustini-Fustini et al. Eur J Endocrin 1999, 140:111-129). Estrogen may also have important effects on the vascular wall. Estradiol and progesterone receptors have been identified in arterial endothelial and smooth muscle cells (Campisi D et al. Int J Tiss React 1987, IX(5):393-398). Estrogens act on the wall of the artery to relax vascular smooth muscle and to decrease vascular resistance. The mechanism appears to be through stimulation of endothelial-derived relaxing factors and an endogenous nitrate (Warren MP and Kulak J Clin Obs Gyn 1998 41(4):976-987). The relaxation induced by 17B-estradiol may play an important role in the regulation of coronary tone, which reduces the risk of coronary disease in postmenopausal women. The production of nitric oxide is mediated by the estrogen receptor, because when the receptor is blocked by an antiestrogen agent, nitric oxide is suppressed.

Several studies have shown that estrogen therapy reduces the risk of heart disease by up to 50% (most recently reviewed by Mendelsohn ME and Karas RH New Engl J Med

1999, 340(23):1801-1811;Rich-Edwards JW N Engl J Med, 1995, 332:1758-1765; Gerhard M, Ganz P, Circulation, 1995, 92:5-8; Grodstein F, et al N Engl J Med 1997, 336:1769-75; Chasen-Taber L and Stampfer MJ Ann of Int Med, 1998, 128:467-477; Warren MP and Kulak J Clin Obstet Gyn 1998, 41(4):976-987). Loss of estrogen may be one of the most important factors in the development of cardiovascular disease in women.

While there is no direct evidence that estrogen prevents atherogenesis, considerable epidemiologic evidence exists that suggests that estrogens may have some benefit in reducing cardiovascular disease: (1) In all age groups, women have a lower incidence of cardiovascular disease than do men; (2) women who undergo a premature surgical menopause and do not take estrogens are twice as likely to have cardiovascular disease are age-matched premenopausal controls; (3) postmenopausal women who use estrogens have a significantly lower incidence of cardiovascular disease compared with those who do not; and (4) women with coronary artery disease detected by angiography have a higher survival rate if they are estrogen users.

In recent years, reports of favorable effects of estrogen therapy on cardiovascular morbidity and mortality have led to enthusiasm for widespread use of estrogens by postmenopausal women (Meinertz T Herz 1997, 22: 151-157). Guidelines for estrogen therapy issued by the American College of Physicians include the statement "Women who have coronary heart disease are likely to benefit from hormone therapy."

More than 30 prospective studies and 13 case controlled studies have examined the effect of estrogen replacement therapy on cardiovascular incidence or prevalence and all cause mortality (Stampfer MJ et al. New Engl J Med 1991, 325:756-62; Grady D et al. Ann Intern Med 1992, 117:1016-37). The majority of these studies showed lower morbidity and mortality from coronary heart disease among users of postmenopausal estrogens than among non-users. Specifically, they have shown that coronary artery disease in estrogen takers is approximately 50% that in women who do not take estrogen. Overall, the bulk of the evidence strongly supports a protective effect of estrogens yielding a relative risk of 0.56 (95% confidence interval 0.50-0.61). However, a "healthy woman selection bias" is present in these studies and potentially may confound these results (estrogen takers have better weight control, exercise more, and smoke less than women who are not prescribed estrogen). Moreover, other biases such as estrogen takers tend to have higher education, higher income, etc., are confounding these epidemiologic studies (Abrams J Clin Cardiol 1998, 21:218-222).

Since the earlier observational trials were not randomized, it is believed by many that as much as 25% of this 50% reduction in risk is due to these various methodological biases

(Barrett-Conner E and Grady D 1998, Ann Rev Public Health 19:55-72). Recently, 2 meta-analyses estimated the reduction in coronary heart disease associated with estrogen use to be in the range of 35 to 44 %, respectively (Grodstein F and Stampfer MJ Prog Cardiol Dis 1995, 38: 199-210; Barrett-Conner E and Grady D 1998, Annu Rev Public Health 19:55-72). Recent studies are exploring the issue of opposed vs unopposed estrogen, because of a documented increased risk for uterine cancer in women with an intact uterus who are taking estrogen alone. The new lines of evidence are suggesting that women taking estrogen plus a progestin (usually a medroxyprogesterone acetate) do not receive an equivalent benefit from the cardioprotective effects compared to women taking estrogen alone (Hulley S et al 1998 JAMA 280:605-613; Abrams J Clin Cardiol 1998, 21:218-222).

The loss of estrogen at menopause is associated with a 6% decline in HDL cholesterol levels and a 5% rise in LDL cholesterol levels, which may explain the higher cardiovascular disease rate among postmenopausal women compared with premenopausal women. The lower incidence of cardiovascular disease among postmenopausal women who take estrogen may be explained in part by the resultant 15% to 19% decrease in LDL cholesterol levels and the 16% to 18% increase in HDL cholesterol levels (JAMA 1995, 273:199-208). The PEPI (Postmenopausal Estrogen/Progestin Intervention, a randomized, double-blind placebo-controlled trial, showed that HDL cholesterol levels rose significantly more in women assigned to estrogen alone than in women assigned the combined estrogen (JAMA 1995, 273:199-208). Recent non-human primates studies substantiate these findings (Clarkson TB Lab An Sci 1998, 48(6):569-72). Statistical modeling of the effect of estrogen on lipid profiles indicates that 25 – 50% of the apparent cardioprotection due to estrogen is mediated by favorable changes in HDL-cholesterol (Bush TL et al. 1987 Circulation 75:1102-9; Gruchow HW et al. 1988 Am Heart J 115:954-63).

Estrogen replacement therapy is not without risk. For years, studies have shown a 3-4-fold increased risk of venous thromboembolism (VTE) in users of oral contraceptives compared to non-users (Weiss G Am J Obstet Gynecol 1999 180:S295-301). One study has shown that intrinsic coagulation factors play a significant role in oral contraceptive-associated VTE (Vandenbroucke JP et al. Lancet 1994 344:1453-7; Rosing J et al. Br J Haematol 1997, 97:233-238). The Factor V Leiden mutation increases risk of VTE 5-10 fold in non users, but 30-fold in third-generation oral contraceptive users. Combined estrogens appear to induce resistance to the body's natural anticoagulation system (APC). Heterozygotes for the Factor V Leiden mutation who take oral contraceptives develop APC resistance as high as that seen in women who are homozygous.

Estrogens increase the risk of endometrial carcinoma approximately 6-fold, an effect that is eliminated, for the most part, by the addition of progestins (Barrett-Conner E and Grady D 1998, Ann Rev Public Health 19:55-72). Controversy continues over whether estrogen replacement increases the risk of breast cancer, but some studies indicate risk is elevated by as much as 30%. (Greendale GA et al. Lancet 1999, 353:571-80).

A number of prospective randomized studies designed to definitely establish whether estrogen replacement therapy reduces the risk of cardiovascular disease in women and whether it increases the risk of breast cancer, are underway. One recently completed trial (HERS – Heart and Estrogen/progestin Replacement Study) compared continuous combined estrogen plus medroxyprogesterone acetate to placebo in 2700 women with pre-existing coronary disease (Hully S et al. 1998 JAMA 280(7):605-13). Compared to controls, the intervention group had significantly more heart disease events in year one of the trial, but significantly fewer events in years 4 and 5 of the trial. Moreover, a significant increase in the rate of thromboembolic events occurred in the early years of the study in women taking hormones. Based on these results, hormone replacement therapy is not recommended for secondary prevention of heart disease.

Two other large, ongoing clinical trials on primary prevention of cardiovascular disease using estrogens are underway. The Women's Health Initiative, due to be completed in 2005 and a U.K. study called WIS-DOM, due to be completed in 2010, should shed new light on the protective effects of estrogen on cardiovascular disease (Meisler JG Jour Women's Health 1999, 8(1):51-5).

In summary, ongoing research suggests that estrogen replacement therapy, particularly involving recently formulated designer estrogens or SERMs, may have beneficial effects on the cardiovascular system as well as bone, without the untoward effects on breast and endometrial tissue. Caution still needs to be observed, nonetheless. Women who take estrogens are, on average, better educated, healthier, have higher incomes and have better access to health care. These differences rather than the estrogens may account for much of the lower risk of heart disease.

For postmenopausal women without frank disease, estrogen replacement therapy appears to have a beneficial effect when one considers the magnitude, consistency, and biological plausibility of the data. For women with pre-existing disease, questions remain as to the safety and efficacy of exogenous estrogens as protective agents against cardiovascular disease.

Estrogen and autoimmune diseases

A. Systemic Lupus Erythematosus

There is a widely held view that estrogens play a role in Systemic lupus erythematosus because:

1. Women of child bearing age are nine times more likely to develop systemic lupus erythematosus than men. Prior to pubescence the rate is three fold higher in females, while post menopausal women have an equal chance of developing SLE as aged matched males. Many studies have been done that show that the reason for the differences in the sexes is probably estrogen related (Lahita R.G., 1986: Springer Seminars in Immunopathology 9, 305-314; Krammer, G.M. and Tsokos, G.C. , 1998 Clinical Immunology and Immunopathology 89: 192-195; Rider at al., 1998 Clinical Immunology and Immunopathology 89: 171-180).

Clues to the role of estrogens in SLE came from studies that concluded that oral contraceptives adversely affected the morbidity of this illness (Buton, J.P., 1996 Ann. Med. Interne, 147:259-264; Julkunen, 1991: Scan. J. Rheumatol. 20:427-433).

2. Patients with Klinefelter syndrome (XXY), have been reported with SLE (Stern et al., 1977: Arthritis and Rheumatism 20:18-22).

3. Patients with SLE have anti-estrogen antibodies (Feldman, 1987: Biochem. Biophys. Acta, 145:1342-1348: Bucala et al., 1987: Clin. Exp. Immunol. 67:167-175)

In the past, oral contraceptives have been shown to cause flare ups of SLE, their use was discouraged in women with SLE, while the current thinking is that the lower dose birth control pills are safe for SLE patients (Julkunen HA *Scand J Rheumatol* 1991;20(6):427-33). As well hormone replacement therapy is considered safe for SLE patients (Mok et al., *Scand J Rheumatol* 1998;27(5):342-6: Kreidstein et al., 1997, *J Rheumatol* 1997 Nov;24(11):2149-52)

4. The estrogen antagonist tamoxofin seems to improve the course of the disease (Sthoeger, 1997, *Ann N Y Acad Sci* 1997 Apr 5;815:367-8: Sthoeger, 1994, *J Rheumatol* 1994 Dec;21(12):2231-8).

B. Estrogen, Rheumatoid Arthritis (RA) and osteoarthritis

The literature surrounding the involvement of estrogens in Rheumatoid arthritis is less clear than with osteoarthritis. Epidemiological studies suggests that RA is influenced by female sex hormones, by one study states that the use of oral contraceptives may postpone the onset of RA, but that estrogens alone no not alleviate the symptoms of RA (Bijlsma *Am J Reprod Immunol* 1992 Oct-Dec;28(3-4):231-4). Adjuvant oestrogen treatment does increase

bone mineral density in postmenopausal women with RA, and may protect against osteophoresis which is often a complication of RA (van den Brink: *Ann Rheum Dis* 1993 Apr;52(4):302-5). While the study mentioned above indicated that estrogens did not alleviate RA symptoms, another study concluded that adjuvant estrogen therapy did not even improve the symptoms. One polymorphism has been reported in the estrogen receptor that seems to be associated with the age of onset of RA (Ushiyama *Ann Rheum Dis* 1999 Jan;58(1):7-10)

Osteoarthritis on the other hand is less prevalent in postmenopausal women who take estrogen replacement therapy (ERT) (Felson *Curr Opin Rheumatol* 1998 May;10(3):269-72) suggesting that ERT may be beneficial in preventing osteoarthritis.

C. Estrogen and Osteophorosis

Osteophorosis is a metabolic bone disorder that leads to bone fragility and subsequent risk of fracture. Treatment for postmenopausal women with osteophoresis includes hormone replacement, in particular estrogen. Estrogen has shown to reduce the incidence of bone loss and fractures (Weiss et al., *N Engl J Med* 1980 Nov 20;303(21):1195-8 :Paganini-Hill et al., *Ann Intern Med* 1981 Jul;95(1):28-31: Ettinger et al., *Ann Intern Med* 1985 Mar;102(3):319-24)

Further, polymorphisms in the estrogen receptor have been associated with bone loss in both humans and mice.(Kobayashi *J Bone Miner Res* 1996 Mar;11(3):306-11 : Kurabayashi *Am J Obstet Gynecol* 1999 May;180(5):1115-20; Deng *Hum Genet* 1998 Nov;103(5):576-85)

Estrogens and Cognitive function

Compared with men, women are at greater risk of developing Alzheimer's disease. Several studies show that women who take estrogen after menopause have a lower incidence of Alzheimer's disease. Among women with Alzheimer's, those taking estrogen suffer less severe symptoms and slower mental deterioration. The duration of estrogen use also seems to be important in reducing risk. Women with a history of long-term use (more than 10 years) had the lowest risk. But even women who took estrogen for a short time also benefited.

Estrogen and breast cancer

The major risk factors for the development of breast cancer are sex, age, family history of breast cancer, age of menarche, age at first full-term pregnancy, and age of menopause. All of these factors, with the exception of family history, have been shown to be directly associated with lifetime exposure to estrogen, increased hormone exposure being

associated with increased risk of developing breast cancer. The increased cancer risk is believed to be caused by an estrogen receptor-mediated proliferative response in cells of the mammary epithelium.

Tamoxifen, an estrogen receptor antagonist, has been shown to be an effective agent for both the prevention and treatment of breast cancer. Using immunohistochemical methods, it is possible to classify breast tumors as being estrogen receptor positive or negative, depending upon the amount of estrogen receptor protein expressed in the tissue. Estrogen receptor positive tumors are more likely to respond to treatment with tamoxifen than estrogen receptor negative tumors. Pre-menopausal women are more likely to develop estrogen receptor negative breast cancers than are post-menopausal women.

Mutations altering the structure and function of the estrogen receptor have been described in primary breast tumors or breast cancer cell lines. It is not clear however whether these changes are primary (and involved in the processes leading to carcinogenesis) or secondary (and a consequence of genetic instability in cancer tissues). In addition to these somatic mutations, some studies have pointed to a possible association between inherited DNA sequence changes and the development of breast cancer, but these studies are also controversial.

Further evidence for the role of estrogen receptors in breast cancer comes from the recent finding that the gene BRCA1, which when inherited in a mutant form predisposes to the development of breast cancer, inhibits estrogen receptor signaling.

Estrogens and endometrial cancer

Carcinoma of the endometrium is the most common pelvic malignancy in women, however because in approximately 75% of cases it is confined to the body of the uterus at the time of diagnosis, it can usually be cured by hysterectomy. Unopposed exposure of endometrial cells to estrogens dramatically increases the chance of developing this form of uterine cancer and it is for this reason that hormone replacement therapy consisting solely of estrogen should not be given to women with intact uteri. Cyclical or continuous co-administration of progesterone serves to prevent excessive proliferation of endometrial cells, reducing the risk of endometrial cancer in post-menopausal women receiving estrogen as part of hormone replacement therapy regimens.

The majority of cases of endometrial cancers express estrogen receptor and, in general, estrogen responsive tumors have a favorable prognosis. Acquired (somatic)

mutations have been described in up to 8.5% of cases, however the role of these mutations in the development and progression of endometrial cancer is uncertain at present.

Although it remains somewhat controversial, studies suggest that use of tamoxifen may increase the chance of developing endometrial cancer. This may be because, in addition to its role in estrogen receptor blockade, tamoxifen has partial receptor agonist activity and results in low-grade induction of estrogen responsive genes that induce endometrial proliferation.

Given the involvement of the estrogen receptor in mediating/modulating various disorders, it is critical to identify sequence polymorphisms in the estrogen receptor and to correlate these with disease states, therapeutic effectiveness and the like. The present invention advances the art by providing a variety of previously unidentified polymorphisms in the ESR-alpha protein.

SNPs

The genomes of all organisms undergo spontaneous mutation in the course of their continuing evolution, generating variant forms of progenitor sequences (Gusella, Ann. Rev. Biochem. 55, 831-854 (1986)). The variant form may confer an evolutionary advantage or disadvantage relative to a progenitor form or may be neutral. In some instances, a variant form confers a lethal disadvantage and is not transmitted to subsequent generations of the organism. In other instances, a variant form confers an evolutionary advantage to the species and is eventually incorporated into the DNA of many or most members of the species and effectively becomes the progenitor form. Additionally, the effect of a variant form may be both beneficial and detrimental, depending on the circumstances. For example, a heterozygous sickle cell mutation confers resistance to malaria, but a homozygous sickle cell mutation is usually lethal. In many instances, both progenitor and variant form(s) survive and co-exist in a species population. The coexistence of multiple forms of a sequence gives rise to polymorphisms, such as SNPs.

The reference allelic form is arbitrarily designated and may be, for example, the most abundant form in a population, or the first allelic form to be identified, and other allelic forms are designated as alternative, variant or polymorphic alleles. The allelic form occurring most frequently in a selected population is sometimes referred to as the "wild type" form.

Approximately 90% of all polymorphisms in the human genome are single nucleotide polymorphisms (SNPs). SNPs are single base pair positions in DNA at which different alleles, or alternative nucleotides, exist in some population. The SNP position, or SNP site, is usually preceded by and followed by highly conserved sequences of the allele (e.g.,

sequences that vary in less than 1/100 or 1/1000 members of the populations). An individual may be homozygous or heterozygous for an allele at each SNP position. As defined by the present invention, the least frequent allele at a SNP position can have any frequency that is less than the frequency of the more frequent allele, including a frequency of less than 1% in a population. A SNP can, in some instances, be referred to as a "cSNP" to denote that the nucleotide sequence containing the SNP is an amino acid coding sequence.

A SNP may arise due to a substitution of one nucleotide for another at the polymorphic site. Substitutions can be transitions or transversions. A transition is the replacement of one purine nucleotide by another purine nucleotide, or one pyrimidine by another pyrimidine. A transversion is the replacement of a purine by a pyrimidine, or vice versa. A SNP may also be a single base insertion/deletion variant (referred to as "indels"). A substitution that changes a codon coding for one amino acid to a codon coding for a different amino acid is referred to as a non-synonymous codon change, or missense mutation. A synonymous codon change, or silent mutation, is one that does not result in a change of amino acid due to the degeneracy of the genetic code. A nonsense mutation is a type of non-synonymous codon change that results in the formation of a stop codon, thereby leading to premature termination of a polypeptide chain and a defective protein.

SNPs, in principle, can be bi-, tri-, or tetra- allelic. However, tri- and tetra-allelic polymorphisms are extremely rare, almost to the point of non-existence (Brookes, Gene 234 (1999) 177-186). For this reason, SNPs are often referred to as "bi-allelic markers", or "di-allelic markers".

Causative SNPs are those SNPs that produce alterations in gene expression or in the expression or function of a gene product, and therefore are most predictive of a possible clinical phenotype. One such class includes SNPs falling within regions of genes encoding a polypeptide product, i.e. cSNPs. These SNPs may result in an alteration of the amino acid sequence of the polypeptide product (i.e., non-synonymous codon changes) and give rise to the expression of a defective or other variant protein. Furthermore, in the case of nonsense mutations, a SNP may lead to premature termination of a polypeptide product. Such variant products can result in a pathological condition, e.g., genetic disease. Examples of genes in which a polymorphism within a coding sequence gives rise to genetic disease include sickle cell anemia and cystic fibrosis. Causative SNPs do not necessarily have to occur in coding regions; causative SNPs can occur in any region that can ultimately affect the expression and/or activity of the protein encoded by the nucleic acid. Such gene areas include those involved in transcription, such as SNPs in promoter regions, in gene areas involved in

transcript processing, such as SNPs at intron-exon boundaries that may cause defective splicing, or SNPs in mRNA processing signal sequences such as polyadenylation signal regions. For example, a SNP may inhibit splicing of an intron and result in mRNA containing a premature stop codon, leading to a defective protein. Consequently, SNPs in regulatory regions can have substantial phenotypic impact.

Some SNPs that are not causative SNPs nevertheless are in close association with, and therefore segregate with, a disease-causing sequence. In this situation, the presence of the SNP correlates with the presence of, or susceptibility to, the disease. These SNPs are invaluable for diagnostics and disease susceptibility screening.

Clinical trials have shown that patient response to treatment with pharmaceuticals is often heterogeneous. Thus there is a need for improved approaches to pharmaceutical agent design and therapy. SNPs can be used to help identify patients most suited to therapy with particular pharmaceutical agents (this is often termed "pharmacogenomics"). Pharmacogenomics can also be used in pharmaceutical research to assist the drug selection process. (Linder et al. (1997), Clinical Chemistry, 43, 254; Marshall (1997), Nature Biotechnology, 15, 1249; International Patent Application WO 97/40462, Spectra Biomedical; and Schafer et al. (1998), Nature Biotechnology, 16, 3.).

Population Studies

Population Genetics is the study of how Mendel's laws and other genetic principles apply to entire populations. Such a study is essential to a proper understanding of evolution because, fundamentally, evolution is the result of progressive change in the genetic composition of a population. Population genetics thus seeks to understand and to predict the effects of such genetic phenomena as segregation, recombination, and mutation; at the same time, population genetics must take into account such ecological and evolutionary factors as population size, patterns of mating, geographic distribution of individuals, migration and natural selection.

Ideally, one would wish to know how to describe the types and frequencies of genes in a population, to explain how the population's genetic composition came to be the way it is, and to predict how the population would change as a result of natural selection or as a result of artificial selection.

In order to explain many of those issues it is important to understand the existing relation between loci denominated: Linkage.

Linkage is the coinheritance of two or more nonallelic genes because their loci are in close proximity on the same chromosome, such that after meiosis they remain associated more often than the 50% expected for unlinked genes. During meiosis, there is a physical crossing over, it is clear that during the production of germ cells there is a physical exchange of maternal and paternal genetic contributions between individual chromatids. This exchange necessarily separates genes in chromosomal regions that were contiguous in each parent and, by mixing them with retained linear order, results in "recombinants". The process of forming recombinants through meiotic crossing-over is an essential feature in the reassortment of genetic traits and is central to understanding the transmission of genes.

Recombination generally occurs between large segments of DNA. This means that contiguous stretches of DNA and genes are likely to be moved together. Conversely, regions of the DNA that are far apart on a given chromosome are likely to become separated during the process of crossing-over.

It is possible to use molecular markers to clarify the recombination events that take place during meiosis. Some markers as (CA)n repeats of different lengths are dispersed throughout human DNA and there is little selective pressure in their lengths are used as position markers and regional identifying characters along chromosomes. Those markers can be used to distinguish paternally derived from maternally derived gene regions.

Other markers are Single Nucleotide Polymorphism (SNP), those are biallelic markers, also used to analyzed the transmission of those markers to offspring.

The pattern of a set of markers along a chromosome is referred to as a "Haplotype". Therefore sets of alleles on the same small chromosomal segment tend to be transmitted as a block through a pedigree. By analyzing the haplotypes in a series of offspring of parents whose haplotypes are known, it is possible to establish which parental segment of which chromosome was transmitted to which child. When not broken up by recombinations, haplotypes can be treated for mapping purposes as alleles at a single highly polymorphic locus.

The existance of a preferential occurrence of a disease gene in association with specific alleles of linked markers is called "Linkage Disequilibrium"(LD). This sort of disequilibrium generally implies that most of the disease chromosomes carry the same mutation and the markers being tested are quite close to the disease gene. For example, there is considerable linkage disequilibrium across the entire HLA locus. The A3 allele is in LD with the B7 and B14 alleles, and as a result B7 and B14 are also highly associated with hemochromatosis. Thus, HLA typing alone can significantly alter the estimate of risk for

hemochromatosis, even if other family members are not available for formal linkage analysis. As a result, using a combination of several markers surrounding the presumptive location of the gene, a haplotype can be determined for affected and unaffected family members.

SNP-Based Association Analysis and Linkage Disequilibrium Mapping

SNPs are useful in association studies for identifying particular SNPs, or other polymorphisms, associated with pathological conditions, such as breast cancer. Association studies may be conducted within the general population and are not limited to studies performed on related individuals in affected families (linkage studies). An association study using SNPs involves determining the frequency of the SNP allele in many patients with the disorder of interest, such as breast cancer, as well as controls of similar age and race. The appropriate selection of patients and controls is critical to the success of SNP association studies. Therefore, a pool of individuals with well-characterized phenotypes is extremely desirable. For example, blood pressure and heart rate can be correlated with SNP patterns in hypertensive individuals in whom these physiological parameters are known in order to find associations between particular SNP genotypes and known phenotypes. Significant associations between particular SNPs or SNP haplotypes and phenotypic characteristics can be determined by standard statistical methods. Association analysis can either be direct or LD based. In direct association analysis, causative SNPs are tested that are candidates for the pathogenic sequence itself.

In LD based SNP association analysis, random SNPs are tested over a large genomic region, possibly the entire genome, in order to find a SNP in LD with the true pathogenic sequence or pathogenic SNP. For this approach, high density SNP maps are required in order for random SNPs to be located close enough to an unknown pathogenic locus to be in linkage disequilibrium with that locus in order to detect an association. SNPs tend to occur with great frequency and are spaced uniformly throughout the genome. The frequency and uniformity of SNPs means that there is a greater probability, compared with other types of polymorphisms such as tandem repeat polymorphisms, that a SNP will be found in close proximity to a genetic locus of interest. SNPs are also mutationally more stable than tandem repeat polymorphisms, such as VNTRs. LD-based association studies are capable of finding a disease susceptibility gene without any a priori assumptions about what or where the gene is.

Currently, however, it is not feasible to do SNP association studies over the entire human genome, therefore candidate genes associated with breast cancer are targeted for SNP identification and association analysis. The candidate gene approach uses a priori knowledge

of disease pathogenesis to identify genes that are hypothesized to directly influence development of the disease. The candidate gene approach may focus on a gene that is directly targeted by a drug used to treat the disorder. To discover SNPs associated with an increased susceptibility to breast cancer, candidate genes can be selected from systems physiologically implicated in the disease pathway. SNPs found in these genes are then tested for statistical association with disease in individuals who have the disease compared with appropriate controls. The candidate gene approach has the advantages of drastically reducing the number of candidate SNPs, and the number of individuals, that need to be typed, compared with LD-based association studies of random SNPs over large areas of, or complete, genomes. Furthermore, in the candidate gene approach, no assumptions are made about the extent of LD over any particular area of the genome.

Combined with the use of a high density map of appropriately spaced, sufficiently informative SNP markers, association studies, including linkage disequilibrium-based genome wide association studies, will enable the identification of most genes involved in complex disorders, such as breast cancer. This will enhance the selection of candidate genes most likely to contain causative SNPs associated with a particular disease. All of the SNPs disclosed by the present invention can be employed as part of genome-wide association studies or as part of candidate gene association studies.

The present invention advances the state of the art and provides commercially useful embodiments by providing previously unidentified SNPs in the estrogen receptor genes.

SUMMARY OF THE INVENTION

The present invention is based on sequencing genomic DNA from human chromosome 6 and cDNAs to define the genomic structure of estrogen receptor alpha genes, novel polymorphisms in the estrogen receptor gene/protein and previously unknown haplotypes. Such polymorphisms/haplotypes can lead to a variety of disorders that are mediated/modulated by a variant estrogen receptor, such as a susceptibility to cancer, osteoporosis, cardiovascular disorders, etc. Based on this sequencing approach, the present invention provides genomic nucleotide sequences, cDNA sequences, amino acid sequences, sequence polymorphisms in the ESR-alpha gene, haplotypes of these polymorphisms, methods of detecting these sequences/polymorphisms in a sample, methods of determining a risk of having or developing a disorder mediated by a variant estrogen receptor and methods of screening for compounds used to treat disorders mediated by a variant estrogen receptor.

DESCRIPTION OF THE FIGURES

Figure 1. Complete genomic sequence of the estrogen receptor alpha gene.

Figure 2. Sequence polymorphisms found in the ESR-alpha genomic DNA (nucleotide position is based on the sequence provided in Figure 1.)

a) SNPs in Liverpool clinical tissue samples.

b) SNPs in Coriell Diversity panels.

c) PCR primers.

d) Sequencing primers.

Figure 3. Amino acid sequence of the estrogen receptor alpha protein.

Figure 4. Estrogen Receptor Haplotypes (See Haplotype Section).

Figure 5. The domain structure of the ESR1 protein and the positions of the SNPs disclosed herein.

Figure 6. The distribution and frequency of many of the SNPs of the present invention.

Figure 7. A graphic representation of the human ESR1 locus.

(a) complete structure of the human estrogen receptor alpha (ERα). Exons are represented by filled boxes and introns by horizontal lines.

(b) Order and names of contigs used to complete the genomic sequence. GA numbers represent Celera contig numbers. Research Genetics BAC clones are represented by standard plate and well numbering.

Figure 8. ESR-alpha SNPs: a) in Coriell Samples, b) in Liverpool Samples (T= tumor sample, B= blood sample).

Figure 9. ESR-alpha exons with SNPs. (see Figure 2 for "N", "C", "I", "A", "S" representations). Underlined sequences indicate the primer sequences.

DETAILED DESCRIPTION OF THE INVENTION

General Description

The present invention is based on sequencing genomic DNA from human chromosome 6 and cDNAs to define the genomic structure of estrogen receptor alpha genes and novel polymorphisms and haplotypes in the estrogen receptor gene/protein. Such polymorphisms/haplotypes can lead to a variety of disorders that are mediated/modulated by a variant estrogen receptor, such as a susceptibility to cancer, osteoporosis, cardiovascular disorders, etc. Based on this sequencing approach, the present invention provides genomic

nucleotide sequences, cDNA sequences, amino acid sequences and sequence polymorphisms/haplotypes in the ESR-alpha gene, methods of detecting these sequences/polymorphisms/haplotypes in a sample, methods of determining a risk of having or developing a disorder mediated by a variant estrogen receptor and methods of screening for compounds used to treat disorders mediated by a variant estrogen receptor.

Isolated SNP-Containing Nucleic Acid Molecules

The present invention provides isolated nucleic acid molecules that contain one or more SNPs disclosed by the present invention. The present invention further provides isolated nucleic acid molecules that encode the variant protein. Such nucleic acid molecules will consist of, consist essentially of, or comprise one or more SNPs of the present invention. The nucleic acid molecule can have additional nucleic acid residues, such as nucleic acid residues that are naturally associated with it or heterologous nucleotide sequences.

As used herein, an "isolated" SNP-containing nucleic acid molecule is one that contains a SNP of the present invention and is separated from other nucleic acid present in the natural source of the nucleic acid. Generally, the isolated SNP-containing nucleic acid, as used herein, will be comprised of one or more SNP positions disclosed by the present invention with flanking nucleotide sequence on either side of the SNP positions. Preferably the flanking sequence is up to about 300 bases, 100 bases, 50 bases, 30 bases, 15 bases, 10 bases, or 4 bases on either side of a SNP position for detection reagents or as long as the entire protein encoding sequence if it is to be used to produce a protein containing the coding variants disclosed in Figures. The important point is that the nucleic acid is isolated from remote and unimportant flanking sequences and is of appropriate length such that it can be subjected to the specific manipulations or uses described herein such as recombinant expression, preparation of probes and primers for the SNP position, and other uses specific to the SNP-containing nucleic acid sequences.

Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule containing a SNP of the present invention, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. However, the nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. For example, recombinant DNA molecules contained in a vector are considered isolated. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the isolated SNP-containing DNA molecules of the present

invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically.

Isolated SNP-containing nucleic acid molecules can be in the form of RNA, such as mRNA, or in the form DNA, including cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The nucleic acid, especially DNA, can be double-stranded or single-stranded. Single-stranded nucleic acid can be the coding strand (sense strand) or the non-coding strand (anti-sense strand).

The present invention further provides related nucleic acid molecules that hybridize under stringent conditions to the nucleic acid molecules disclosed herein. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences encoding a peptide at least 60-70% homologous to each other typically remain hybridized to each other. The conditions can be such that sequences at least about 60%, at least about 70%, or at least about 80%, or at least about 90% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. One example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45 °C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65 °C. Examples of moderate to low stringency hybridization conditions are well known in the art.

Specific Embodiments

Peptide Molecules

The present invention provides nucleic acid sequences that encode variants of the estrogen receptor. These variant molecule/sequences will be referred to herein as the estrogen receptor variants of the present invention, the estrogen receptor proteins of the present invention, or peptides/proteins of the present invention.

The present invention provides isolated estrogen receptor protein molecules that consist of, consist essentially of or are comprised of the amino acid sequences of the estrogen receptor variant proteins disclosed herein.

As used herein, a protein or peptide is said to be "isolated" or "purified" when it is substantially free of cellular material or free of chemical precursors or other chemicals. The peptides of the present invention can be purified to homogeneity or other degrees of purity. The level of purification will be based on the intended use. The critical feature is that the preparation

allows for the desired function of the peptide, even if in the presence of considerable amounts of other components.

In some uses, "substantially free of cellular material" includes preparations of the peptide having less than about 30% (by dry weight) other proteins (i.e., contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins. When the peptide is recombinantly produced, it can also be substantially free of culture medium, i.e., culture medium represents less than about 20% of the volume of the protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of the peptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the estrogen receptor protein having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

The isolated estrogen receptor proteins can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. For example, a nucleic acid molecule encoding the estrogen receptor protein is cloned into an expression vector, the expression vector introduced into a host cell and the protein expressed in the host cell. The protein can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques. Many of these techniques are described in detail below.

Accordingly, the present invention provides proteins that consist of the amino acid sequences summarized in Figure 1, including one or more of the sequence polymorphisms provided in Figure 2. A protein consists of an amino acid sequence when the amino acid sequence is the final amino acid sequence of the protein.

The present invention further provides proteins that consist essentially of the amino acid sequences summarized in Figure 1, including one or more of the sequence polymorphisms provided in Figure 2. A protein consists essentially of an amino acid sequence when such an amino acid sequence is present with only a few additional amino acid residues in the final protein.

The present invention further provides a protein that is comprised of the amino acid sequences summarized in Figure 1, including one or more of the sequence polymorphisms provided in Figure 2. A protein is comprised of an amino acid sequence when the amino acid

sequence is at least part of the final amino acid sequence of the protein. In such a fashion, the protein can be only the peptide or have additional amino acid molecules, such as amino acid residues (contiguous encoded sequence) that are naturally associated with it or heterologous amino acid residues/peptide sequences. Such a protein can have a few additional amino acid residues or can comprise several hundred or more additional amino acids. A brief description of how various types of these proteins can be made/isolated is provided below.

The estrogen receptor protein of the present invention can be attached to heterologous sequences to form chimeric or fusion proteins. Such chimeric and fusion proteins comprise a estrogen receptor protein operatively linked to a heterologous protein having an amino acid sequence not substantially homologous to the estrogen receptor protein. "Operatively linked" indicates that the estrogen receptor protein and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the estrogen receptor protein.

In some uses, the fusion protein does not affect the activity of the estrogen receptor protein *per se*. For example, the fusion protein can include, but is not limited to, enzymatic fusion proteins, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, MYC-tagged, HI-tagged and Ig fusions. Such fusion proteins, particularly poly-His fusions, can facilitate the purification of recombinant estrogen receptor protein. In certain host cells (e.g., mammalian host cells), expression and/or secretion of a protein can be increased by using a heterologous signal sequence.

A chimeric or fusion protein can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different protein sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST protein). A estrogen receptor protein-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the estrogen receptor protein.

Polypeptides often contain amino acids other than the 20 amino acids commonly referred to as the 20 naturally-occurring amino acids. Further, many amino acids, including the terminal amino acids, may be modified by natural processes, such as processing and other

post-translational modifications, or by chemical modification techniques well known in the art. Common modifications that occur naturally in polypeptides are described in basic texts, detailed monographs, and the research literature, and they are well known to those of skill in the art. Accordingly, the polypeptides also encompass derivatives or analogs in which a substituted amino acid residue is not one encoded by the genetic code, in which a substituent group is included, in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or in which the additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence for purification of the mature polypeptide or a pro-protein sequence.

Known modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

Such modifications are well-known to those of skill in the art and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as *Proteins - Structure and Molecular Properties*, 2nd Ed., T.E. Creighton, W. H. Freeman and Company, New York (1993). Many detailed reviews are available on this subject, such as by Wold, F., *Posttranslational Covalent Modification of Proteins*, B.C. Johnson, Ed., Academic Press, New York 1-12 (1983); Seifter *et al.* (*Meth. Enzymol. 182*: 626-646 (1990)) and Rattan *et al.* (*Ann. N.Y. Acad. Sci. 663*:48-62 (1992)).

The present invention further provides fragments of the estrogen receptor proteins of the present invention, in addition to proteins and peptides that comprise and consist of such fragments. The fragments to which the invention pertains, however, are not to be construed as encompassing fragments that may be disclosed publicly prior to the present invention.

As used herein, a fragment comprises at least 8 or more contiguous amino acid residues from a estrogen receptor protein. Such fragments can be chosen based on the ability to retain

one or more of the biological activities of the estrogen receptor protein or could be chosen for the ability to perform a function, e.g. act as an immunogen. Particularly important fragments are biologically active fragments, peptides which are, for example, about 8 or more amino acids in length, that contain a variant amino acid residue (Figure 2). Such fragments will typically comprise a domain or motif of the estrogen receptor proteins of the present invention, e.g., active site, ligand binding domain or DNA binding domain. Further, possible fragments include, but are not limited to, domain or motif containing fragments, soluble peptide fragments, and fragments containing immunogenic structures. Predicted domains and functional sites are readily identifiable by computer programs well-known and readily available to those of skill in the art (e.g., PROSITE analysis).

Protein/Peptide Uses

The proteins of the present invention can be used in assays to determine the biological activity of the protein, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its binding partner or receptor) in biological fluids; and as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state). Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products. Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

The estrogen receptor proteins of the present invention are useful for biological assay. Such assays involve any of the known estrogen receptor functions or activities or properties useful for the diagnosis and treatment of estrogen receptor-related conditions.

The estrogen receptor proteins of the present invention are also useful in drug screening assays, in cell-based or cell-free systems. Cell-based systems can be native, i.e., cells that normally express the receptor protein, as a biopsy or expanded in cell culture. In one embodiment, however, cell-based assays involve recombinant host cells expressing the receptor protein.

The estrogen receptor proteins of the present invention can be used to identify compounds that modulate receptor activity. Both the estrogen receptor protein of the present invention and appropriate fragments can be used in high-throughput screens to assay candidate compounds for the ability to bind and/or modulate the activity of the receptor. These compounds can be further screened against a functional receptor to determine the effect of the compound on the receptor activity. Further, these compounds can be tested in animal or invertebrate systems to determine activity/effectiveness. Compounds can be identified that activate (agonist) or inactivate (antagonist) the receptor to a desired degree. Such compounds can be selected for the ability to act on one or more of the variant estrogen receptor proteins of the present invention.

Further, the receptor polypeptides can be used to screen a compound for the ability to stimulate or inhibit interaction between the receptor protein and a target molecule that normally interacts with the receptor protein, e.g. estrogen. The target can be ligand or a binding partner that the receptor protein normally interacts (for example, an estrogen ligand or a DNA sequence). Such assays typically include the steps of combining the receptor protein with a candidate compound under conditions that allow the receptor protein, or fragment, to interact with the target molecule, and to detect the formation of a complex between the protein and the target or to detect the biochemical consequence of the interaction with the receptor protein and the target, such as any of the associated effects of DNA binding or signal transduction.

Candidate compounds include, for example, 1) peptides such as soluble peptides, including Ig-tailed fusion peptides and members of random peptide libraries (see, e.g., Lam *et al.*, *Nature 354*:82-84 (1991); Houghten *et al.*, *Nature 354*:84-86 (1991)) and combinatorial chemistry-derived molecular libraries made of D- and/or L- configuration amino acids; 2) phosphopeptides (e.g., members of random and partially degenerate, directed phosphopeptide libraries, see, e.g., Songyang *et al.*, *Cell 72*:767-778 (1993)); 3) antibodies (e.g., polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, and single chain antibodies as well as Fab, $F(ab')_2$, Fab expression library fragments, and epitope-binding fragments of antibodies); and 4) small organic and inorganic molecules (e.g., molecules obtained from combinatorial and natural product libraries).

One candidate compound is a soluble fragment of the receptor that competes for ligand binding. Other candidate compounds include mutant receptors or appropriate fragments containing mutations that affect receptor function and thus compete for ligand. Accordingly, a fragment that competes for ligand, for example with a higher affinity, or a fragment that binds ligand but does not allow release, is encompassed by the invention.

The invention further includes other end point assays to identify compounds that modulate (stimulate or inhibit) receptor activity. The assays typically involve an assay of events in the signal transduction pathway that indicate receptor activity. Thus, the expression of genes that are up- or down-regulated in response to the receptor protein dependent signal cascade can be assayed. In one embodiment, the regulatory region of such genes can be operably linked to a marker that is easily detectable, such as luciferase. Alternatively, phosphorylation of the receptor protein, or a receptor protein target, could also be measured. Any of the biological or biochemical functions mediated by the receptor can be used as an endpoint assay. These include all of the biochemical or biochemical/biological events described herein, in the references cited herein, incorporated by reference for these endpoint assay targets, and other functions known to those of ordinary skill in the art.

The receptor polypeptides are also useful in competition binding assays in methods designed to discover compounds that interact with the receptor. Thus, a compound is exposed to a receptor polypeptide under conditions that allow the compound to bind or to otherwise interact with the polypeptide. Ligands to the receptor is also added to the mixture. If the test compound interacts with the receptor or ligand, it decreases the amount of complex formed or activity from the receptor target. This type of assay is particularly useful in cases in which compounds are sought that interact with specific regions of the receptor.

To perform cell free drug screening assays, it is sometimes desirable to immobilize either the receptor protein, or fragment, or its target molecule to facilitate separation of complexes from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay.

Techniques for immobilizing proteins on matrices can be used in the drug screening assays. In one embodiment, a fusion protein can be provided which adds a domain that allows the protein to be bound to a matrix. For example, glutathione-S-transferase/15625 fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the cell lysates (e.g., ^{35}S-labeled) and the candidate compound, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads are washed to remove any unbound label, and the matrix immobilized and radiolabel determined directly, or in the supernatant after the complexes are dissociated. Alternatively, the complexes can be dissociated from the matrix, separated by SDS-PAGE, and the level of receptor-binding protein found in the bead fraction quantitated from the gel using standard electrophoretic techniques. For example, either the polypeptide or its target molecule can be

immobilized utilizing conjugation of biotin and streptavidin using techniques well known in the art. Alternatively, antibodies reactive with the protein but which do not interfere with binding of the protein to its target molecule can be derivatized to the wells of the plate, and the protein trapped in the wells by antibody conjugation. Preparations of a receptor-binding protein and a candidate compound are incubated in the receptor protein-presenting wells and the amount of complex trapped in the well can be quantitated. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the receptor protein target molecule, or which are reactive with receptor protein and compete with the target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the target molecule.

Agents that modulate the protein of the present invention can be identified using one or more of the above assays, alone or in combination. It is generally preferable to use a cell-based or cell free system first and then confirm activity in an animal or other model system. Such model systems are well known in the art and can readily be employed in this context.

Modulators of receptor protein activity identified according to these drug screening assays can be used to treat a subject with a disorder mediated by the receptor pathway, by treating cells that express the estrogen receptor protein. These methods of treatment include the steps of administering the modulators of protein activity in a pharmaceutical composition as described herein, to a subject in need of such treatment.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., an estrogen receptor modulating agent, an antisense estrogen receptor nucleic acid molecule, an estrogen receptor-specific antibody, or an estrogen receptor-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

The estrogen receptor proteins of the present invention are also useful to provide a target for diagnosing a disease or predisposition to disease mediated by the estrogen receptor. Accordingly, the invention provides methods for detecting the presence, or levels of, the estrogen receptor variants of the present invention (or encoding mRNA) in a cell, tissue, or

organism. The method involves contacting a biological sample with a compound capable of interacting with the receptor protein (or gene or mRNA encoding the receptor) such that the interaction can be detected.

One agent for detecting a protein in a sample is an antibody capable of selectively binding to a variant form of the estrogen receptor protein. Such samples include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

The estrogen receptor proteins of the present invention also provide targets for diagnosing active disease, or predisposition to disease, in a patient having a variant estrogen receptor, particularly a disease involving the estrogen pathway, such as bone growth, cell differentiation, etc. Thus, the receptor can be isolated from a biological sample and assayed for the presence of a genetic mutation that results in aberrant receptor activity. This includes amino acid substitution, deletion, insertion, rearrangement, (as the result of aberrant splicing events), and inappropriate post-translational modification as provided in Figure 2. Analytic methods include altered electrophoretic mobility, altered tryptic peptide digest, altered receptor activity in cell-based or cell-free assay, alteration in ligand or antibody-binding pattern, altered isoelectric point, direct amino acid sequencing, and any other of the known assay techniques useful for detecting mutations in a protein. Particularly useful are the variation provided in Figure 2.

In vitro techniques for detection of peptide include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. Alternatively, the peptide can be detected *in vivo* in a subject by introducing into the subject a labeled anti-peptide antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. Particularly useful are methods that detect the specific allelic variants of the estrogen receptor disclosed herein that are expressed in a subject and methods which detect fragments of a peptide in a sample.

The peptides are also useful in pharmacogenomic analysis. Pharmacogenomics deal with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, e.g., Eichelbaum, M. (*Clin. Exp. Pharmacol. Physiol.* 23(10-11) :983-985 (1996)), and Linder, M.W. (*Clin. Chem.* 43(2):254-266 (1997)). The clinical outcomes of these variations result in severe toxicity of therapeutic drugs in certain individuals or therapeutic failure of drugs in certain individuals as a result of individual variation in metabolism. Thus, the genotype of the individual can determine the way a therapeutic compound acts on the body or the way the body metabolizes the compound.

Further, the activity of drug metabolizing enzymes effects both the intensity and duration of drug action. Thus, the pharmacogenomics of the individual permit the selection of effective compounds and effective dosages of such compounds for prophylactic or therapeutic treatment based on the individual's genotype. The discovery of genetic polymorphisms in some drug metabolizing enzymes has explained why some patients do not obtain the expected drug effects, show an exaggerated drug effect, or experience serious toxicity from standard drug dosages. Polymorphisms can be expressed in the phenotype of the extensive metabolizer and the phenotype of the poor metabolizer. Accordingly, genetic polymorphism may lead to allelic protein variants of the receptor protein in which one or more of the receptor functions in one population is different from those in another population. The peptides thus allow a target to ascertain a genetic predisposition that can affect treatment modality. Thus, in a ligand-based treatment, polymorphism may give rise to amino terminal extracellular domains and/or other ligand-binding regions that are more or less active in ligand binding, and receptor activation. Accordingly, ligand dosage would necessarily be modified to maximize the therapeutic effect within a given population containing a polymorphism/haplotype. As an alternative to genotyping, specific polymorphic peptides could be identified.

Antibodies

The invention also provides antibodies that selectively bind to the estrogen receptor proteins of the present invention as well as fragments thereof. As used herein, an antibody selectively binds a target protein when it binds the target protein and does not significantly bind to unrelated proteins. An antibody is still considered to selectively bind a protein even if it also binds to other proteins that are not substantially homologous with the target protein so long as such proteins share homology with a fragment or domain of the protein target of the antibody. In this case, it would be understood that antibody binding to the protein is still selective despite some degree of cross-reactivity.

As used herein, an antibody is defined in terms consistent with that recognized within the art: they are multi-subunit proteins produced by a mammalian organism in response to an antigen challenge. The antibodies of the present invention include polyclonal antibodies and monoclonal antibodies, as well as fragments of such antibodies, including, but not limited to, Fab or $F(ab')_2$, and Fv fragments.

Many methods are known for generating and/or identifying antibodies to a given target peptide. Several such methods are described by Harlow, Antibodies, Cold Spring Harbor Press, (1989). In general, to generate antibodies, an isolated peptide is used as an immunogen and is

administered to a mammalian organism, such as a rat, rabbit or mouse. The full-length protein, an antigenic peptide fragment or a fusion protein can be used.

Antibodies are preferably prepared from regions or discrete fragments of the estrogen receptor protein. Antibodies can be prepared from any region of the peptide as described herein. However, preferred regions will include those involved in function/activity and/or receptor/binding partner interaction. An antigenic fragment will typically comprise at least 10 contiguous amino acid residues. The antigenic peptide can comprise, however, at least 12, 14, 20 or more amino acid residues. Such fragments can be selected on a physical property, such as fragments correspond to regions that are located on the surface of the protein, e.g., hydrophilic regions or can be selected based on sequence uniqueness.

Detection on an antibody of the present invention can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Antibody Uses

The antibodies can be used to isolate the estrogen receptor protein of the present invention by standard techniques, such as affinity chromatography or immunoprecipitation. The antibodies can facilitate the purification of the natural protein from cells and recombinantly produced protein expressed in host cells. In addition, such antibodies are useful to detect the presence of the estrogen receptor protein of the present invention in cells or tissues to determine the pattern of expression of the protein among various tissues in an organism and over the course of normal development. Further, such antibodies can be used to detect protein *in situ, in vitro,* or in a cell lysate or supernatant in order to evaluate the abundance and pattern of expression. Also, such antibodies can be used to assess abnormal tissue distribution or abnormal expression

during development. Antibody detection of circulating fragments of the full length estrogen receptor protein can be used to identify turnover.

Further, the antibodies can be used to assess expression in disease states such as in active stages of the disease or in an individual with a predisposition toward disease related to the protein's function, particularly diseases involving bone growth/formation/degeneration. When a disorder is caused by an inappropriate tissue distribution, developmental expression, level of expression of the protein, or expressed/processed form, the antibody can be prepared against the normal protein. If a disorder is characterized by a specific mutation in the protein, antibodies specific for this mutant protein can be used to assay for the presence of the specific mutant protein.

The antibodies can also be used to assess normal and aberrant subcellular localization of cells in the various tissues in an organism. The diagnostic uses can be applied, not only in genetic testing, but also in monitoring a treatment modality. Accordingly, where treatment is ultimately aimed at correcting the expression level or the presence of aberrant sequence and aberrant tissue distribution or developmental expression, antibodies directed against the protein or relevant fragments can be used to monitor therapeutic efficacy.

Additionally, antibodies are useful in pharmacogenomic analysis. Thus, antibodies prepared against polymorphic proteins can be used to identify individuals that require modified treatment modalities. The antibodies are also useful as diagnostic tools as an immunological marker for aberrant estrogen receptor protein analyzed by electrophoretic mobility, isoelectric point, tryptic peptide digest, and other physical assays known to those in the art.

The antibodies are also useful for inhibiting protein function, for example, blocking the binding of the estrogen receptor protein to a binding partner such as a ligand. These uses can also be applied in a therapeutic context in which treatment involves inhibiting the protein's function. An antibody can be used, for example, to block binding, thus modulating (agonizing or antagonizing) the peptides activity. Antibodies can be prepared against specific fragments containing sites required for function or against intact protein that is associated with a cell or cell membrane.

The invention also encompasses kits for using antibodies to detect the presence of a protein in a biological sample. The kit can comprise antibodies such as a labeled or labelable antibody and a compound or agent for detecting estrogen receptor protein in a biological sample; means for determining the amount of protein in the sample; means for comparing the amount of estrogen receptor protein in the sample with a standard; and instructions for use.

Nucleic Acid Molecules

The present invention further provides isolated nucleic acid molecules that encode any of the estrogen receptor proteins of the present invention. Such nucleic acid molecules will consist of, consist essentially of, or comprise a nucleotide sequence that encodes one of the estrogen receptor proteins of the present invention.

As used herein, an "isolated" nucleic acid molecule is one that is separated from other nucleic acid present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. However, there can be some flanking nucleotide sequences, for example up to about 5KB, 4KB, 3KB, 2KB, or 1KB or less, particularly contiguous peptide encoding sequences and peptide encoding sequences within the same gene but separated by introns in the genomic sequence. The important point is that the nucleic acid is isolated from remote and unimportant flanking sequences such that it can be subjected to the specific manipulations described herein such as recombinant expression, preparation of probes and primers, and other uses specific to the nucleic acid sequences.

Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. However, the nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated.

For example, recombinant DNA molecules contained in a vector are considered isolated. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the isolated DNA molecules of the present invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically.

Accordingly, the present invention provides nucleic acid molecules that consist of the nucleotide sequences shown in Figure 1, including one or more of the sequence polymorphisms provided in Figure 2. A nucleic acid molecule consists of a nucleotide sequence when the nucleotide sequence is the complete nucleotide sequence of the nucleic acid molecule.

The present invention further provides nucleic acid molecules that consist essentially of the nucleotide sequence shown in Figure 1, including one or more of the sequence polymorphisms provided in Figure 2. A nucleic acid molecule consists essentially of a

nucleotide sequence when such a nucleotide sequence is present with only a few additional nucleic acid residues in the final nucleic acid molecule.

The present invention further provides nucleic acid molecules that are comprised of the nucleotide sequences shown in Figure 1, including one or more of the sequence polymorphisms provided in Figure 2. A nucleic acid molecule is comprised of a nucleotide sequence when the nucleotide sequence is at least part of the final nucleotide sequence of the nucleic acid molecule. In such a fashion, the nucleic acid molecule can be only the nucleotide sequence or have additional nucleic acid residues, such as nucleic acid residues that are naturally associated with it or heterologous nucleotide sequences. Such a nucleic acid molecule can have a few additional nucleotides or can comprises several hundred or more additional nucleotides. A brief description of how various types of these nucleic acid molecules can be readily made/isolated is provided below.

The isolated nucleic acid molecules can encode the mature protein plus additional amino or carboxyl-terminal amino acids, or amino acids interior to the mature peptide (when the mature form has more than one peptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, facilitate protein trafficking, prolong or shorten protein half-life or facilitate manipulation of a protein for assay or production, among other things. As generally is the case *in situ*, the additional amino acids may be processed away from the mature protein by cellular enzymes.

As mentioned above, the isolated nucleic acid molecules include, but are not limited to, the sequence encoding the estrogen receptor protein alone, the sequence encoding the mature peptide and additional coding sequences, such as a leader or secretory sequence (e.g., a pre-pro or pro-protein sequence), the sequence encoding the mature peptide, with or without the additional coding sequences, plus additional non-coding sequences, for example introns and non-coding 5' and 3' sequences such as transcribed but non-translated sequences that play a role in transcription, mRNA processing (including splicing and polyadenylation signals), ribosome binding and stability of mRNA, as well as genomic regulatory sequences such as promoters. In addition, the nucleic acid molecule may be fused to a marker sequence encoding, for example, a peptide that facilitates purification.

Isolated nucleic acid molecules can be in the form of RNA, such as mRNA, or in the form DNA, including cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The nucleic acid, especially DNA, can be double-stranded or single-stranded. Single-stranded nucleic acid can be the coding strand (sense strand) or the non-coding strand (anti-sense strand).

The invention further provides nucleic acid molecules that encode fragments of the proteins of the present invention. A fragment comprises a contiguous nucleotide sequence greater than 12 or more nucleotides. Further, a fragment could at least 30, 40, 50, 100, 250 or 500 nucleotides in length. The length of the fragment will be based on its intended use. For example, the fragment can encode epitope bearing regions of the peptide, or can be useful as DNA probes and primers. Such fragments can be isolated using the known nucleotide sequence to synthesize an oligonucleotide probe. A labeled probe can then be used to screen a cDNA library, genomic DNA library, or mRNA to isolate nucleic acid corresponding to the coding region. Further, primers can be used in PCR reactions to clone specific regions of gene.

A probe/primer typically comprises substantially a purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides.

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences encoding a peptide at least 50-55% homologous to each other typically remain hybridized to each other. The conditions can be such that sequences at least about 65%, at least about 70%, or at least about 75% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. One example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65C.

Nucleic Acid Molecule Uses

The nucleic acid molecules of the present invention are useful for probes, primers, chemical intermediates, and in biological assays. The probe can correspond to any sequence along the entire length of the nucleic acid molecules provided in Figure 1, including one or more of the sequence polymorphisms provided in Figure 2. Accordingly, it could be derived from 5' noncoding regions, the coding region, and 3' noncoding regions. However, as discussed, fragments are not to be construed as encompassing fragments disclosed prior to the present invention.

The nucleic acid molecules are also useful as primers for PCR to amplify any given region of a nucleic acid molecule and are useful to synthesize antisense molecules of desired length and sequence.

The nucleic acid molecules are also useful for constructing recombinant vectors. Such vectors include expression vectors that express a portion of, or all of, the peptide sequences. Vectors also include insertion vectors, used to integrate into another nucleic acid molecule sequence, such as into the cellular genome, to alter *in situ* expression of a gene and/or gene product. For example, an endogenous coding sequence can be replaced via homologous recombination with all or part of the coding region containing one or more specifically introduced mutations.

The nucleic acid molecules are also useful for expressing antigenic portions of the proteins.

The nucleic acid molecules are also useful for designing ribozymes corresponding to all, or a part, of the mRNA produced from the nucleic acid molecules described herein.

The nucleic acid molecules are also useful for constructing host cells expressing a part, or all, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful for constructing transgenic animals expressing all, or a part, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful for making vectors that express part, or all, of the peptides.

The nucleic acid molecules are also useful as hybridization probes for determining the presence, level, form and distribution of nucleic acid expression. Accordingly, the probes can be used to detect the presence of, or to determine levels of, a specific nucleic acid molecule in cells, tissues, and in organisms. The nucleic acid whose level is determined can be DNA or RNA. Accordingly, probes corresponding to the peptides described herein can be used to assess expression and/or gene copy number in a given cell, tissue, or organism. These uses are relevant for diagnosis of disorders involving an increase or decrease in estrogen receptor protein expression relative to normal results.

In vitro techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detecting DNA include Southern hybridizations and *in situ* hybridization.

Probes can be used as a part of a diagnostic test kit for identifying cells or tissues that express a estrogen receptor proteins of the present invention, such as by measuring a level of a

receptor-encoding nucleic acid in a sample of cells from a subject e.g., mRNA or genomic DNA, or determining if a receptor gene has been mutated.

Nucleic acid expression assays are useful for drug screening to identify compounds that modulate estrogen receptor nucleic acid expression.

The invention thus provides a method for identifying a compound that can be used to treat a disorder associated with nucleic acid expression of the estrogen receptor gene. The method typically includes assaying the ability of the compound to modulate the expression of the estrogen receptor nucleic acid and thus identifying a compound that can be used to treat a disorder characterized by undesired estrogen receptor nucleic acid expression. The assays can be performed in cell-based and cell-free systems. Cell-based assays include cells naturally expressing the estrogen receptor nucleic acid or recombinant cells genetically engineered to express specific nucleic acid sequences.

The assay for estrogen receptor nucleic acid expression can involve direct assay of nucleic acid levels, such as mRNA levels, or on collateral compounds involved in the signal pathway. Further, the expression of genes that are up- or down-regulated in response to the estrogen receptor protein signal pathway can also be assayed. In this embodiment the regulatory regions of these genes can be operably linked to a reporter gene such as luciferase.

Thus, modulators of estrogen receptor gene expression can be identified in a method wherein a cell is contacted with a candidate compound and the expression of mRNA determined. The level of expression of estrogen receptor mRNA in the presence of the candidate compound is compared to the level of expression of estrogen receptor mRNA in the absence of the candidate compound. The candidate compound can then be identified as a modulator of nucleic acid expression based on this comparison and be used, for example to treat a disorder characterized by aberrant nucleic acid expression. When expression of mRNA is statistically significantly greater in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of nucleic acid expression. When nucleic acid expression is statistically significantly less in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of nucleic acid expression.

The invention further provides methods of treatment, with the nucleic acid as a target, using a compound identified through drug screening as a gene modulator to modulate estrogen receptor nucleic acid expression. Modulation includes both up-regulation (i.e. activation or agonization) or down-regulation (suppression or antagonization) or nucleic acid expression.

Alternatively, a modulator for estrogen receptor nucleic acid expression can be a small molecule or drug identified using the screening assays described herein as long as the drug or small molecule inhibits the estrogen receptor nucleic acid expression.

The nucleic acid molecules are also useful for monitoring the effectiveness of modulating compounds on the expression or activity of the estrogen receptor gene in clinical trials or in a treatment regimen. Thus, the gene expression pattern can serve as a barometer for the continuing effectiveness of treatment with the compound, particularly with compounds to which a patient can develop resistance. The gene expression pattern can also serve as a marker indicative of a physiological response of the affected cells to the compound. Accordingly, such monitoring would allow either increased administration of the compound or the administration of alternative compounds to which the patient has not become resistant. Similarly, if the level of nucleic acid expression falls below a desirable level, administration of the compound could be commensurately decreased.

The nucleic acid molecules are also useful in diagnostic assays for qualitative changes in estrogen receptor nucleic acid, and particularly in qualitative changes that lead to pathology. The nucleic acid molecules can be used to detect mutations in estrogen receptor genes and gene expression products such as mRNA. The nucleic acid molecules can be used as hybridization probes to detect naturally-occurring genetic mutations in the estrogen receptor gene and thereby to determine whether a subject with the mutation is at risk for a disorder caused by the mutation. Mutations include deletion, addition, or substitution of one or more nucleotides in the gene, chromosomal rearrangement, such as inversion or transposition, modification of genomic DNA, such as aberrant methylation patterns or changes in gene copy number, such as amplification. Detection of a mutated form of the estrogen receptor gene associated with a dysfunction provides a diagnostic tool for an active disease or susceptibility to disease when the disease results from overexpression, underexpression, or altered expression of a estrogen receptor protein.

Individuals carrying mutations in the estrogen receptor gene can be detected at the nucleic acid level by a variety of techniques. Genomic DNA can be analyzed directly or can be amplified by using PCR prior to analysis. RNA or cDNA can be used in the same way. In some uses, detection of the mutation involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran *et al.*, *Science 241*:1077-1080 (1988); and Nakazawa *et al.*, *PNAS 91*:360-364 (1994)), the latter of which can be particularly useful for detecting point mutations in the gene (see Abravaya *et al.*, *Nucleic*

Acids Res. 23:675-682 (1995)). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a gene under conditions such that hybridization and amplification of the gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. Deletions and insertions can be detected by a change in size of the amplified product compared to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to normal RNA or antisense DNA sequences.

Alternatively, mutations in a estrogen receptor gene can be directly identified, for example, by alterations in restriction enzyme digestion patterns determined by gel electrophoresis.

Further, sequence-specific ribozymes (U.S.Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site. Perfectly matched sequences can be distinguished from mismatched sequences by nuclease cleavage digestion assays or by differences in melting temperature.

Sequence changes at specific locations can also be assessed by nuclease protection assays such as RNase and S1 protection or the chemical cleavage method. Furthermore, sequence differences between a mutant estrogen receptor gene and a wild-type gene can be determined by direct DNA sequencing. A variety of automated sequencing procedures can be utilized when performing the diagnostic assays ((1995) *Biotechniques 19*:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen *et al., Adv. Chromatogr. 36*:127-162 (1996); and Griffin *et al., Appl. Biochem. Biotechnol. 38*:147-159 (1993)).

Other methods for detecting mutations in the gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA duplexes (Myers *et al., Science 230*:1242 (1985)); Cotton *et al., PNAS 85*:4397 (1988); Saleeba *et al., Meth. Enzymol. 217*:286-295 (1992)), electrophoretic mobility of mutant and wild type nucleic acid is compared (Orita *et al., PNAS 86*:2766 (1989); Cotton *et al., Mutat. Res. 285*:125-144 (1993); and Hayashi *et al., Genet. Anal. Tech. Appl. 9*:73-79 (1992)), and movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (Myers *et al., Nature 313*:495 (1985)). Examples of other techniques for detecting point mutations include, selective oligonucleotide hybridization, selective amplification, and selective primer extension.

The nucleic acid molecules are also useful for testing an individual for a genotype that while not necessarily causing the disease, nevertheless affects the treatment modality. Thus, the nucleic acid molecules can be used to study the relationship between an individual's genotype and the individual's response to a compound used for treatment (pharmacogenomic relationship). Accordingly, the nucleic acid molecules described herein can be used to assess the mutation content of the estrogen receptor gene in an individual in order to select an appropriate compound or dosage regimen for treatment.

Thus nucleic acid molecules displaying genetic variations that affect treatment provide a diagnostic target that can be used to tailor treatment in an individual. Accordingly, the production of recombinant cells and animals containing these polymorphism/haplotypes allow effective clinical design of treatment compounds and dosage regimens.

The nucleic acid molecules are thus useful as antisense constructs to control estrogen receptor gene expression in cells, tissues, and organisms. A DNA antisense nucleic acid molecule is designed to be complementary to a region of the gene involved in transcription, preventing transcription and hence production of estrogen receptor protein. An antisense RNA or DNA nucleic acid molecule would hybridize to the mRNA and thus block translation of mRNA into estrogen receptor protein.

Alternatively, a class of antisense molecules can be used to inactivate mRNA in order to decrease expression of estrogen receptor nucleic acid. Accordingly, these molecules can treat a disorder characterized by abnormal or undesired estrogen receptor nucleic acid expression. This technique involves cleavage by means of ribozymes containing nucleotide sequences complementary to one or more regions in the mRNA that attenuate the ability of the mRNA to be translated. Possible regions include coding regions and particularly coding regions corresponding to the catalytic and other functional activities of the estrogen receptor proteins of the present invention, such as ligand binding.

The nucleic acid molecules also provide vectors for gene therapy in patients containing cells that are aberrant in estrogen receptor gene expression. Thus, recombinant cells, which include the patient's cells that have been engineered *ex vivo* and returned to the patient, are introduced into an individual where the cells produce the desired estrogen receptor protein to treat the individual.

The invention also encompasses kits for detecting the presence of a estrogen receptor nucleic acid in a biological sample. For example, the kit can comprise reagents such as a labeled or labelable nucleic acid or agent capable of detecting estrogen receptor nucleic acid in a biological sample; means for determining the amount of estrogen receptor nucleic acid in the

sample; and means for comparing the amount of estrogen receptor nucleic acid in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect estrogen receptor protein mRNA or DNA.

Design of SNP-Containing Nucleic Acids Detection Methods

The SNP-containing nucleic acid molecules of the present invention are useful as probes, primers, chemical intermediates, and in biological assays for SNPs of the present invention. The probes/primers can correspond to one or more of the SNPs provided in Figure 2 or can correspond to a specific region 5' and/or 3' to a SNP position. However, as discussed above, fragments are not to be construed as encompassing fragments that are not associated with SNPs of the present invention or those known in the art for SNP detection. The SNP-containing nucleic acid molecules and information provided herein are also useful for designing primers for PCR to amplify any given SNP of the present invention and to design any formatted SNP detection reagent/kits.

A probe/primer typically comprises substantially a purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides. Depending on the particular application, the consecutive nucleotides can either include the target SNP position, or be a specific region in close enough proximity 5' and/or 3' to the SNP position to carry out the desired assay.

Preferred primer and probe sequences can readily be determined using the sequences provided in Figures 1, 2, and 9. It will be apparent to one of skill in the art that such primers and probes are useful as diagnostic probes or amplification primers for genotyping SNPs of the present invention, and can be incorporated into a kit format.

For analyzing SNPs, it may be appropriate to use oligonucleotides specific to alternative SNP alleles (referred to as "allele-specific oligonucleotides", "allele-specific probes", or "allele-specific primers"). The design and use of allele-specific probes for analyzing polymorphisms is described by e.g., Saiki et al., Nature 324, 163-166 (1986); Dattagupta, EP 235,726, Saiki, WO 89/11548.

In a hybridization-based assay, allele-specific probes can be designed that hybridize to a segment of target DNA from one individual but do not hybridize to the corresponding segment from another individual due to the presence of different polymorphic forms in the respective segments from the two individuals. Hybridization conditions should be sufficiently stringent that there is a significant difference in hybridization intensity between alleles, and

preferably an essentially binary response, whereby a probe hybridizes to only one of the alleles. Some probes are designed to hybridize to a segment of target DNA such that the polymorphic site aligns with a central position (e.g., in a 15-mer at the 7 position; in a 16-mer, at either the 8 or 9 position) of the probe. This design of probe achieves good discrimination in hybridization between different allelic forms.

Allele-specific probes are often used in pairs, the "pairs" may be identical except for a one nucleotide mismatch that represents the allelic variants at the SNP position. One member of a pair perfectly matches a reference form of a target sequence and the other member perfectly matches a variant form. In the case of an array, several pairs of probes can then be immobilized on the same support for simultaneous analysis of multiple polymorphisms within the same target sequence.

In one type of PCR-based assay, an allele-specific primer hybridizes to a site on target DNA overlapping the SNP position and only primes amplification of an allelic form to which the primer exhibits perfect complementarity. See Gibbs, Nucleic Acid Res. 17 2427-2448 (1989). This primer is used in conjunction with a second primer that hybridizes at a distal site. Amplification proceeds from the two-primers, resulting in a detectable product that indicates the particular allelic form is present. A control is usually performed with a second pair of primers, one of which shows a single base mismatch at the polymorphic site and the other of which exhibits perfect complementarity to a distal site. The single-base mismatch prevents amplification and no detectable product is formed. The method works best when the mismatch is included in the 3'-most position of the oligonucleotide aligned with the polymorphism because this position is most destabilizing to elongation from the primer (see, e.g., WO 93/22456). This PCR-based assay can be utilized as part of the TaqMan assay, described below.

<u>SNP Detection Kits, Nucleic Acid Arrays, and Integrated Systems</u>

The present invention further provides SNP detection kits, such as arrays or microarrays of nucleic acid molecules, or probe/primer sets, that are based on the SNPs provided in Figures 1, 2, 8, 9

In one embodiment of the present invention, kits are provided which contain the necessary reagents to carry out one or more assays that detect one or more SNPs disclosed herein. The present invention also provides multicomponent integrated systems for analyzing the SNPs provided by the present invention.

SNP detection kits may contain one or more oligonucleotide probes, or pairs of probes, that hybridize at or near each SNP position. Multiple pairs of allele-specific oligonucleotides may be included in the kit to simultaneously assay large numbers of SNPs, at least one of which is one of the SNPs of the present invention. In some kits, such as arrays, the allele-specific oligonucleotides are provided immobilized to a substrate. For example, the same substrate can comprise allele-specific oligonucleotide probes for detecting at least 1; 10; 100; 1000; 10,000; 100,000; 300,000 or substantially all of the polymorphisms shown in Figures 1, 2, 8 and 9.

Specifically, the invention provides a compartmentalized kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the nucleic acid probes, for example an allele-specific oligonucleotide, that can bind to a fragment of the human genome containing a SNP disclosed herein; and (b) one or more other containers comprising one or more of the following: wash reagents or reagents capable of detecting the presence of a bound probe.

In detail, a compartmentalized kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers, strips of plastic, glass or paper, or arraying material such as silica. Such containers allow one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers may include a container which will accept the test sample, a container which contains the SNP probe, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound probe. The kit can further comprise reagents for PCR or other enzymatic reactions, and instructions for using the kit. One skilled in the art will readily recognize that the previously unidentified SNPs of the present invention can be routinely identified using the sequence information disclosed herein and can be readily incorporated into one of the established kit formats which are well known in the art.

The present invention further provides arrays or microarrays of nucleic acid molecules that are based on the sequence information provided in Figures 1, including one or more of the variations provided in Figure 2.

As used herein “Arrays” or "Microarrays" refers to an array of distinct polynucleotides or oligonucleotides synthesized on a substrate, such as paper, nylon or other type of membrane, filter, chip, glass slide, or any other suitable solid support. In one

embodiment, the microarray is prepared and used according to the methods described in US Patent 5,837,832, Chee et al., PCT application W095/11995 (Chee et al.), Lockhart, D. J. et al. (1996; Nat. Biotech. 14: 1675-1680) and Schena, M. et al. (1996; Proc. Natl. Acad. Sci. 93: 10614-10619), all of which are incorporated herein in their entirety by reference. In other embodiments, such arrays are produced by the methods described by Brown et al., US Patent No. 5,807,522. Arrays or microarrays are commonly referred to as “DNA chips”.

Any number of oligonucleotide probes, such as allele-specific oligonucleotides, may be implemented in an array, wherein each probe or pair of probes corresponds to a different SNP position. The oligonucleotides are synthesized at designated areas on a substrate using a light-directed chemical process. The substrate may be paper, nylon or other type of membrane, filter, chip, glass slide or any other suitable solid support.

Hybridization assays based on oligonucleotide arrays rely on the differences in hybridization stability of short oligonucleotides probes to perfectly matched and mismatched target sequence variants. Efficient access to polymorphism information is obtained through a basic structure comprising high-density arrays of oligonucleotide probes attached to a solid support (e.g., a chip) at selected positions. Each DNA chip can contain thousands to millions of individual synthetic DNA probes arranged in a grid-like pattern and miniaturized to the size of a dime, each corresponding to a particular SNP position or allelic variant. Preferably, probes are attached to a solid support in an ordered, addressable array.

The array/chip technology has already been applied with success in numerous cases. For example, the screening of mutations has been undertaken in the BRCA1 gene, in S. cerevisiae mutant strains, and in the protease gene of HIV- I virus (Hacia et al., 1996; Shoemaker et al., 1996 ; Kozal et al., 1996). Chips of various formats for use in detecting SNPs can be produced on a customized basis.

An array-based tiling strategy useful for detecting SNPs is described in EP 785280. Briefly, arrays may generally be "tiled" for a large number of specific polymorphisms. "Tiling" refers to the synthesis of a defined set of oligonucleotide probes that are made up of a sequence complementary to the target sequence of interest, as well as preselected variations of that sequence, e.g., substitution of one or more given positions with one or more members of the basis set of monomers, i.e. nucleotides. Tiling strategies are further described in PCT application No. WO 95/11995. In a particular aspect, arrays are tiled for a number of specific SNPs. In particular, the array is tiled to include a number of detection blocks, each detection block being specific for a specific SNP or a set of SNPs. For example, a detection block may be tiled to include a number of probes that span the sequence segment that includes a specific

SNP. To ensure probes that are complementary to each allele, the probes are synthesized in pairs differing at the SNP position. In addition to the probes differing at the SNP position, monosubstituted probes are also generally tiled within the detection block. Such methods can readily be applied to the SNP information disclosed herein.

These monosubstituted probes have bases at and up to a certain number of bases in either direction from the polymorphism, substituted with the remaining nucleotides (selected from A, T, G, C and U). Typically the probes in a tiled detection block will include substitutions of the sequence positions up to and including those that are 5 bases away from the SNP. The monosubstituted probes provide internal controls for the tiled array, to distinguish actual hybridization from artefactual cross-hybridization. Upon completion of hybridization with the target sequence and washing of the array, the array is scanned to determine the position on the array to which the target sequence hybridizes. The hybridization data from the scanned array is then analyzed to identify which allele or alleles of the SNP are present in the sample. Hybridization and scanning may be carried out as described in PCT application No. WO 92/10092 and WO 95/11995 and US patent No. 5,424,186.

Thus, in some embodiments, the chips may comprise an array of nucleic acid sequences of fragments of about 15 nucleotides in length. In further embodiments, the chip may comprise an array including at least one of the sequences selected from the group consisting of those disclosed in the Figures1, 2, 8, 9, and the sequences complementary thereto, or a fragment thereof, said fragment comprising at least about 8 consecutive nucleotides, preferably 10, 15, 20, more preferably 25, 30, 40, 47, or 50 consecutive nucleotides and containing a polymorphic base. In some embodiments the polymorphic base is within 5, 4, 3, 2, or 1 nucleotides from the center of the polynucleotide, more preferably at the center of said polynucleotide. In other embodiments, the chip may comprise an array containing any number of polynucleotides of the present invention.

An oligonucleotide may be synthesized on the surface of the substrate by using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application W095/251116 (Baldeschweiler et al.) which is incorporated herein in its entirety by reference. In another aspect, a "gridded" array analogous to a dot (or slot) blot may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedures. An array, such as those described above, may be produced by hand or by using available devices (slot blot or dot blot apparatus), materials (any suitable solid support), and machines (including robotic

instruments), and may contain 8, 24, 96, 384, 1536, 6144 or more oligonucleotides, or any other number which lends itself to the efficient use of commercially available instrumentation.

Using such arrays, the present invention provides methods of identifying the SNPs of the present invention in a sample. Such methods comprise incubating a test sample with an array comprising one or more oligonucleotide probes corresponding to at least one SNP position of the present invention, and assaying for binding of a nucleic acid from the test sample with one or more of the oligonucleotide probes. Such assays will typically involve arrays comprising oligonucleotides probes corresponding to many SNP positions and/or allelic variants of those SNP positions, at least one of which is a SNP of the present invention.

Conditions for incubating a nucleic acid molecule with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid molecule used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or array assay formats can readily be adapted to employ the novel SNPs disclosed herein. Examples of such assays can be found in Chard, T, An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G. R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1 982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice and Theory of Enzyme Immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985).

The test samples of the present invention include, but are not limited to, nucleic acid extracts, cells, and protein or membrane extracts from cells, which may be obtained from any bodily fluids (such as blood, urine, saliva, phlegm, gastric juices, etc.), cultured cells, biopsies, or other tissue preparations. The test sample used in the above-described methods will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods of preparing nucleic acid, protein, or cell extracts are well known in the art and can be readily be adapted in order to obtain a sample that is compatible with the system utilized.

Multicomponent integrated systems may also be used to analyze SNPs. Such systems miniaturize and compartmentalize processes such as PCR and capillary electrophoresis reactions in a single functional device. An example of such technique is disclosed in US patent 5,589,136, which describes the integration of PCR amplification and capillary electrophoresis in chips.

Integrated systems can be envisaged mainly when microfluidic systems are used. These systems comprise a pattern of microchannels designed onto a glass, silicon, quartz, or plastic wafer included on a microchip. The movements of the samples are controlled by electric, electroosmotic or hydrostatic forces applied across different areas of the microchip to create functional microscopic valves and pumps with no moving parts. Varying the voltage controls the liquid flow at intersections between the micro-machined channels and changes the liquid flow rate for pumping across different sections of the microchip.

For genotyping SNPs, the microfluidic system may integrate, for example, nucleic acid amplification, minisequencing primer extension, capillary electrophoresis, and a detection method such as laser induced fluorescence detection.

In a first step, the DNA samples are amplified, preferably by PCR. Then, the amplification products are subjected to automated minisequencing reactions using ddNTPs (specific fluorescence for each ddNTP) and the appropriate oligonucleotide minisequencing primers which hybridize just upstream of the targeted polymorphic base. Once the extension at the 3' end is completed, the primers are separated from the unincorporated fluorescent ddNTPs by capillary electrophoresis. The separation medium used in capillary electrophoresis can be, for example, polyacrylamide, polyethyleneglycol or dextran. The incorporated ddNTPs in the single nucleotide primer extension products are identified by laser-induced fluorescence detection. This microchip can be used to process at least 96 to 384 samples, or more, in parallel.

Vectors/host cells

The invention also provides vectors containing the nucleic acid molecules described herein. The term "vector" refers to a vehicle, preferably a nucleic acid molecule, that can transport the nucleic acid molecules. When the vector is a nucleic acid molecule, the nucleic acid molecules are covalently linked to the vector nucleic acid. With this aspect of the invention, the vector includes a plasmid, single or double stranded phage, a single or double stranded RNA or DNA viral vector, or artificial chromosome, such as a BAC, PAC, YAC, OR MAC.

A vector can be maintained in the host cell as an extrachromosomal element where it replicates and produces additional copies of the nucleic acid molecules. Alternatively, the vector may integrate into the host cell genome and produce additional copies of the nucleic acid molecules when the host cell replicates.

The invention provides vectors for the maintenance (cloning vectors) or vectors for expression (expression vectors) of the nucleic acid molecules. The vectors can function in procaryotic or eukaryotic cells or in both (shuttle vectors).

Expression vectors contain cis-acting regulatory regions that are operably linked in the vector to the nucleic acid molecules such that transcription of the nucleic acid molecules is allowed in a host cell. The nucleic acid molecules can be introduced into the host cell with a separate nucleic acid molecule capable of affecting transcription. Thus, the second nucleic acid molecule may provide a trans-acting factor interacting with the cis-regulatory control region to allow transcription of the nucleic acid molecules from the vector. Alternatively, a trans-acting factor may be supplied by the host cell. Finally, a trans-acting factor can be produced from the vector itself. It is understood, however, that in some embodiments, transcription and/or translation of the nucleic acid molecules can occur in a cell-free system.

The regulatory sequence to which the nucleic acid molecules described herein can be operably linked include promoters for directing mRNA transcription. These include, but are not limited to, the left promoter from bacteriophage λ, the lac, TRP, and TAC promoters from *E. coli*, the early and late promoters from SV40, the CMV immediate early promoter, the adenovirus early and late promoters, and retrovirus long-terminal repeats.

In addition to control regions that promote transcription, expression vectors may also include regions that modulate transcription, such as repressor binding sites and enhancers. Examples include the SV40 enhancer, the cytomegalovirus immediate early enhancer, polyoma enhancer, adenovirus enhancers, and retrovirus LTR enhancers.

In addition to containing sites for transcription initiation and control, expression vectors can also contain sequences necessary for transcription termination and, in the transcribed region a ribosome binding site for translation. Other regulatory control elements for expression include initiation and termination codons as well as polyadenylation signals. The person of ordinary skill in the art would be aware of the numerous regulatory sequences that are useful in expression vectors. Such regulatory sequences are described, for example, in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

A variety of expression vectors can be used to express a nucleic acid molecule. Such vectors include chromosomal, episomal, and virus-derived vectors, for example vectors derived from bacterial plasmids, from bacteriophage, from yeast episomes, from yeast chromosomal elements, including yeast artificial chromosomes, from viruses such as baculoviruses,

papovaviruses such as SV40, Vaccinia viruses, adenoviruses, poxviruses, pseudorabies viruses, and retroviruses. Vectors may also be derived from combinations of these sources such as those derived from plasmid and bacteriophage genetic elements, eg. cosmids and phagemids. Appropriate cloning and expression vectors for prokaryotic and eukaryotic hosts are described in Sambrook *et al., Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

The regulatory sequence may provide constitutive expression in one or more host cells (i.e. tissue specific) or may provide for inducible expression in one or more cell types such as by temperature, nutrient additive, or exogenous factor such as a hormone or other ligand. A variety of vectors providing for constitutive and inducible expression in prokaryotic and eukaryotic hosts are well known to those of ordinary skill in the art.

The nucleic acid molecules can be inserted into the vector nucleic acid by well-known methodology. Generally, the DNA sequence that will ultimately be expressed is joined to an expression vector by cleaving the DNA sequence and the expression vector with one or more restriction enzymes and then ligating the fragments together. Procedures for restriction enzyme digestion and ligation are well known to those of ordinary skill in the art.

The vector containing the appropriate nucleic acid molecule can be introduced into an appropriate host cell for propagation or expression using well-known techniques. Bacterial cells include, but are not limited to, *E. coli*, *Streptomyces*, and *Salmonella typhimurium*. Eukaryotic cells include, but are not limited to, yeast, insect cells such as *Drosophila*, animal cells such as COS and CHO cells, and plant cells.

As described herein, it may be desirable to express the peptide as a fusion protein. Accordingly, the invention provides fusion vectors that allow for the production of the peptides. Fusion vectors can increase the expression of a recombinant protein, increase the solubility of the recombinant protein, and aid in the purification of the protein by acting for example as a ligand for affinity purification. A proteolytic cleavage site may be introduced at the junction of the fusion moiety so that the desired peptide can ultimately be separated from the fusion moiety. Proteolytic enzymes include, but are not limited to, factor Xa, thrombin, and enterokinase. Typical fusion expression vectors include pGEX (Smith *et al.*, *Gene 67*:31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, *Gene 69*:301-315 (1988)) and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology 185*:60-89 (1990)).

Recombinant protein expression can be maximized in a host bacteria by providing a genetic background wherein the host cell has an impaired capacity to proteolytically cleave the recombinant protein. (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Alternatively, the sequence of the nucleic acid molecule of interest can be altered to provide preferential codon usage for a specific host cell, for example *E. coli.* (Wada *et al., Nucleic Acids Res. 20*:2111-2118 (1992)).

The nucleic acid molecules can also be expressed by expression vectors that are operative in yeast. Examples of vectors for expression in yeast e.g., *S. cerevisiae* include pYepSec1 (Baldari, *et al., EMBO J. 6*:229-234 (1987)), pMFa (Kurjan *et al., Cell 30*:933-943(1982)), pJRY88 (Schultz *et al., Gene 54*:113-123 (1987)), and pYES2 (Invitrogen Corporation, San Diego, CA).

The nucleic acid molecules can also be expressed in insect cells using, for example, baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith *et al., Mol. Cell Biol. 3*:2156-2165 (1983)) and the pVL series (Lucklow *et al., Virology 170*:31-39 (1989)).

In certain embodiments of the invention, the nucleic acid molecules described herein are expressed in mammalian cells using mammalian expression vectors. Examples of mammalian expression vectors include pCDM8 (Seed, B. *Nature 329*:840(1987)) and pMT2PC (Kaufman *et al., EMBO J. 6*:187-195 (1987)).

The expression vectors listed herein are provided by way of example only of the well-known vectors available to those of ordinary skill in the art that would be useful to express the nucleic acid molecules. The person of ordinary skill in the art would be aware of other vectors suitable for maintenance propagation or expression of the nucleic acid molecules described herein. These are found for example in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

The invention also encompasses vectors in which the nucleic acid sequences described herein are cloned into the vector in reverse orientation, but operably linked to a regulatory sequence that permits transcription of antisense RNA. Thus, an antisense transcript can be produced to all, or to a portion, of the nucleic acid molecule sequences described herein, including both coding and non-coding regions. Expression of this antisense RNA is subject to each of the parameters described above in relation to expression of the sense RNA (regulatory sequences, constitutive or inducible expression, tissue-specific expression).

The invention also relates to recombinant host cells containing the vectors described herein. Host cells therefore include prokaryotic cells, lower eukaryotic cells such as yeast, other eukaryotic cells such as insect cells, and higher eukaryotic cells such as mammalian cells.

The recombinant host cells are prepared by introducing the vector constructs described herein into the cells by techniques readily available to the person of ordinary skill in the art. These include, but are not limited to, calcium phosphate transfection, DEAE-dextran-mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, lipofection, and other techniques such as those found in Sambrook, *et al.* (*Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Host cells can contain more than one vector. Thus, different nucleotide sequences can be introduced on different vectors of the same cell. Similarly, the nucleic acid molecules can be introduced either alone or with other nucleic acid molecules that are not related to the nucleic acid molecules such as those providing trans-acting factors for expression vectors. When more than one vector is introduced into a cell, the vectors can be introduced independently, co-introduced or joined to the nucleic acid molecule vector.

In the case of bacteriophage and viral vectors, these can be introduced into cells as packaged or encapsulated virus by standard procedures for infection and transduction. Viral vectors can be replication-competent or replication-defective. In the case in which viral replication is defective, replication will occur in host cells providing functions that complement the defects.

Vectors generally include selectable markers that enable the selection of the subpopulation of cells that contain the recombinant vector constructs. The marker can be contained in the same vector that contains the nucleic acid molecules described herein or may be on a separate vector. Markers include tetracycline or ampicillin-resistance genes for prokaryotic host cells and dihydrofolate reductase or neomycin resistance for eukaryotic host cells. However, any marker that provides selection for a phenotypic trait will be effective.

While the mature proteins can be produced in bacteria, yeast, mammalian cells, and other cells under the control of the appropriate regulatory sequences, cell- free transcription and translation systems can also be used to produce these proteins using RNA derived from the DNA constructs described herein.

Where secretion of the peptide is desired, which is difficult to achieve with multi-transmembrane domain containing proteins such as estrogen receptors, appropriate secretion

signals are incorporated into the vector. The signal sequence can be endogenous to the peptides or heterologous to these peptides.

Where the peptide is not secreted into the medium, which is typically the case with estrogen receptors, the protein can be isolated from the host cell by standard disruption procedures, including freeze thaw, sonication, mechanical disruption, use of lysing agents and the like. The peptide can then be recovered and purified by well-known purification methods including ammonium sulfate precipitation, acid extraction, anion or cationic exchange chromatography, phosphocellulose chromatography, hydrophobic-interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography, or high performance liquid chromatography.

It is also understood that depending upon the host cell in recombinant production of the peptides described herein, the peptides can have various glycosylation patterns, depending upon the cell, or maybe non-glycosylated as when produced in bacteria. In addition, the peptides may include an initial modified methionine in some cases as a result of a host-mediated process.

Uses of vectors and host cells

The recombinant host cells expressing the peptides described herein have a variety of uses. First, the cells are useful for producing a estrogen receptor protein or peptide that can be further purified to produce desired amounts of estrogen receptor protein or fragments. Thus, host cells containing expression vectors are useful for peptide production.

Host cells are also useful for conducting cell-based assays involving the estrogen receptor protein or estrogen receptor protein fragments, such as those described above as well as other formats known in the art. Thus, a recombinant host cell expressing a native estrogen receptor protein is useful for assaying compounds that stimulate or inhibit estrogen receptor protein function.

Host cells are also useful for identifying estrogen receptor protein mutants in which these functions are affected. If the mutants naturally occur and give rise to a pathology, host cells containing the mutations are useful to assay compounds that have a desired effect on the mutant estrogen receptor protein (for example, stimulating or inhibiting function) which may not be indicated by their effect on the native estrogen receptor protein.

Genetically engineered host cells can be further used to produce non-human transgenic animals. A transgenic animal is preferably a mammal, for example a rodent, such as a rat or mouse, in which one or more of the cells of the animal include a transgene. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal

develops and which remains in the genome of the mature animal in one or more cell types or tissues of the transgenic animal. These animals are useful for studying the function of a estrogen receptor protein and identifying and evaluating modulators of estrogen receptor protein activity. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians.

A transgenic animal can be produced by introducing nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Any of the estrogen receptor protein nucleotide sequences can be introduced as a transgene into the genome of a non-human animal, such as a mouse.

Any of the regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. This includes intronic sequences and polyadenylation signals, if not already included. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the estrogen receptor protein to particular cells.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of transgenic mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene can further be bred to other transgenic animals carrying other transgenes. A transgenic animal also includes animals in which the entire animal or tissues in the animal have been produced using the homologously recombinant host cells described herein.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al. PNAS 89*:6232-6236 (1992). Another example of a recombinase system is the FLP recombinase system of *S. cerevisiae* (O'Gorman *et al. Science 251*:1351-1355 (1991). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein is required. Such animals can be provided through the construction of

"double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al. Nature 385*:810-813 (1997) and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, e.g., a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_0 phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyst and then transferred to pseudopregnant female foster animal. The offspring born of this female foster animal will be a clone of the animal from which the cell, e.g., the somatic cell, is isolated.

Transgenic animals containing recombinant cells that express the peptides described herein are useful to conduct the assays described herein in an *in vivo* context. Accordingly, the various physiological factors that are present *in vivo* and that could effect ligand binding, estrogen receptor protein activation, and signal transduction, may not be evident from *in vitro* cell-free or cell-based assays. Accordingly, it is useful to provide non-human transgenic animals to assay *in vivo* estrogen receptor protein function, including ligand interaction, the effect of specific mutant estrogen receptor protein on estrogen receptor protein function and ligand interaction, and the effect of chimeric estrogen receptor protein. It is also possible to assess the effect of null mutations, that is mutations that substantially or completely eliminate one or more estrogen receptor protein functions.

EXAMPLES:

1. SNP Identification and Characterization

Individual exons of ESR1 were PCR amplified using primers flanking each adjacent sequence of exon (exon/intron boundaries), and the sequence of amplified fragments was analyzed. As the PCR template, genomic DNA from Coriell Diversity Panels (10 individuals in each of 5 ethnic groups) (see Figure 2 (b)), and/or Liverpool clinical breast tumor and matching blood samples (from tissue obtained in Liverpool, England, see Figure 2 (a)) (48 patients) was used. PolyPhred version 2.0 (D. A. Nickerson, S. Taylor, N. Kolker, Univ. of Washington, 1998) was run on the sequences (with default settings) to visualize potential heterozygotes. Tagged sites were examined for quality to verify polymorphisms.

36 SNPs with a frequency greater than 2 and a quality score greater than 20 were found with 13 being unique to the clinical samples. 15 of the SNPs showed at least one

instance of a change in heterozygosity in the clinical samples, and 4 showed at least one instance of a loss in heterozygosity. For the analysis, PCR primers were used for SNP identification and detection (see Figure 2 (d)).

Additionally, the primer set in Figure 2(c) and M13 primers were used for overlapping PCR and clone sequencing.

Table 1. Summary of SNPs found in the clinical samples. All SNPs had a frequency greater than 2 and a quality score greater than 20 (see Figure 8).

Number of SNPs	39
Number in Liverpool	34
Number in Coriell	26
Number unique to Coriell	5
Number unique in Liverpool	12

Table 2: Summary of changes in heterozygosity in clinical samples. SNPs had a frequency greater than two and a quality score greater than 20 (See Figure 8).

Number of Liverpool SNPs With >1 Change in Heterozygosity	15
Number of Liverpool SNPs With >1 case of Loss of Heterozygosity	4

Figure 5 shows the domain structure of the ESR1 protein and the position of many of the SNPs disclosed herein. Figure 6 provides a graphical representation of the SNPs and frequency of occurance in the samples tested.

Figure 8 (a) shows the SNPs and frequency of occurance in Coriell Samples wherein the samples are collected from Northern European, Chinese, Indo-Pakistani, Africa American and Southwestern Native American ethnic groups. In 3' flanking Exon 8, the positions of the SNPs are based on the sequence of AL078582 that is in Genbank. The result can be used for detection purposes among the specific ethnic groups. Figure 8 (b) shows the SNPs and frequence of occurance in Liverpool samples wherein the samples are selected from the groups of blood samples and breast cancer samples.

2. Haplotype Analysis

The method developed for SNP discovery was designed to recover haplotype data. SNPs could be associated into a specific haplotype. The sample cDNA was from a random population present in unknown proportions. SNPs coming from a specific clone were clustered and built into haplotyes.

Data consist of two sample types. Liverpool samples are from 48 patients, and each patient had a tumor and blood sample typed. Coriell samples were controls, but they were not matched controls. Rather they included a mix of Europeans, Chinese, Indo-Pakistani, and African Americans. 46 SNPs in ESR1 were scored in the Liverpool samples. The same 46 SNPs plus an additional 6 SNPs 3' of the RSR1 gtene were scored in the Coriell sample.

These data were subjected to an analysis to infer the most likely haplotype phase of the individuals. The results appear in Figure 4 (a) where each haplotype has a number and the number after the dash is a count (or frequency) of that haplotype.

Figure 4 (b) is the non-singleton haplotype data that were fitted to a neighbor-joining tree. If a tree were cut at the arrow, the clade including 3L, 10-4, ... 73L would be partitioned from the rest of the tree, as "Clade X". The following table will illustrate a difference in the incidence of tumors in haplotypes on Clade X vs. the rest of the tree. The incidence of each haplotype was first counted by adding the numbers after the dashes, wherein L represented the tumorous Liverpool samples and the non-L represented Coriell controls.

	Clade X	Rest of tree
Tumor	49	64
Control	4	49

A chi-square was calculated based on the 2 x2 table as of 21.29, which, with one degree of freedom that has a probability less than 0.0001. Therefore, the Clade X of the ER1 gene has a much greater chance of being associated with a tumor. This entire clade is so rare elsewhere in the world. Even among Europeans, it was present only once out of 20 haplotypes.

Figure 4 (c) was a reconstructed haplotypes cladogram which indicated a subset of SNPs in ER1 that preserve the property of having clades highly enriched in the tumor samples or the control.

The topmost clade (38L-3 and above) has a count(frequency) of 27 in the Liverpool sample and 2 in the controls. The remainder of the tree has a count of 44 in Liverpool and 54 in Coriell. This 2 x 2 table has a chi-square of 21.095 and $P < 0.0005$. Thus, these 10 SNPs capture most of the informative discriminating alleles in the original 46 SNPs.

The 10 sites that were identified as showing nucleotide frequency differences between Coriell controls and Liverpool are:

5	ESR1-exon 1A170487	
9	ESR1-exon 1C167989	
11	ESR1-exon 1E64331	
17	ESR1-exon Intrn 3	243187
20	ESR1-exon 4	306382
24	ESR1-exon Intrn 6	423220
28	ESR1-exon Intrn 7	460564
29	ESR1-exon 8	460929
35	ESR1-exon 8	461968
45	ESR1-exon 8	54404

<u>3. ESR1 Genomic Sequencing- The Complete Genomic Structure of Estrogen Receptor alpha</u>

Estrogen receptor (ER) is a member of the nuclear hormone receptor gene superfamily. This family of genes is characterized by a modular structure with three distinct domains: a variable (N)-terminal domain, a highly conserved DNA binding domain, and a conserved (C)-terminal domain (reviewed in 1, 2). Functionally, the (N)-terminus domain regulates transactivation, the DNA binding domain regulates dimerization and DNA binding, and the (C)-terminus domain regulates transactivation, dimerization, ligand binding, nuclear translocation, silencing, and Heat Shock Protein binding. It was shown that the functions of the individual domains of the nuclear hormone gene superfamily are independent of the receptor in which they are found, and that the domains retain their function even when placed into different heterologous proteins (3,4,5). The domain modularity in the nuclear hormone receptor gene superfamily exists because the major subfamilies of these genes evolved through a simple gene duplication early in evolution (6). The nuclear hormone receptor gene family can be separated according to two different classification schemes, one based on hormone binding, the other based on dimerization and how the receptors bind to their respective DNA response elements (for a review, see 2).

The cDNA for ERα was first cloned and sequenced from the MCF-7 breast cancer cell line and was found to have 27% identity and 41% conservation to the v-erb-A gene (7). ERα was mapped to chromosome 6q25.1 using Fluorescence In Situ Hybridization (FISH) and chromosome banding (8). In 1996, a novel estrogen receptor (ERβ) was identified by degenerate PCR (9) and mapped to 14q22-24 by FISH (10). ERα and ERβ were shown to have 96% sequence identity in the DNA binding domain, 58% identity in the ligand-binding domain, and low similarity in the 5' and 3' ends as well as in the hinge (domain D). A variety of ERα and ERβ variants have since been described, including single and multiple exon deletions, truncated transcripts, and transcripts containing insertions (11,12,13). These variants were isolated from a variety of sources, including normal tissues, tumor tissues and cell lines. The ER status of tumors in breast cancer patients has been used as an indicator of response to endocrine therapy (14,15), and many studies have examined the role of ER in breast cancer tumor progression, ER-negative status, and hormone antagonist resistance (for a complete review, see 16).

Because of the importance of the ER gene, we set about to clone it in its entirety and determine its complete structure. Initially, we used standard Bacterial Artificial Chromosome (BAC) sequencing to generate sequence information for the coding regions of the genes. As Celera's sequencing of the human genome progressed, the remaining regions of ER were filled in using Celera regional assemblies. A small region of less than 25 kb was filled in on ERα using a public BAC (AI353611.6, positions 1,497-25,941)

Materials and Methods

1) BAC Screening

Appropriate markers were designed for ERα and ERβ exons and used to obtain commercially available BAC clones from Research Genetics (Huntsville, AL). A number of positive BACs were selected and individual clones were re-screened for verification.

2) DNA Isolation and Library Preparation

BAC DNA was isolated from verified clones using QIAGEN columns (QIAGEN, Inc., Valencia, CA) according to the manufacturer's specifications. Shotgun libraries were prepared following standard protocols (17). Briefly, isolated BAC DNA was sonicated, polished, and size fractionated. Size selected DNA fragments were then subcloned into pUC19 using standard ligation techniques. Ligated DNA was transformed into Electrocompetent cells (Life Technologies, Rockville, MD) and grown overnight.

3) DNA Sequencing and Annotation

Sequencing reactions were performed using Big Dye Terminator chemistry (Applied Biosystems, Foster City, CA) and run on an ABI PRISM 3700 DNA Analyzer (Applied Biosystems). Phred (18), Phrap and Consed (19) were used for base calling, assembly, and finishing, respectively. Exon locations were determined using Cross_Match to compare the published gene sequences to the genomic contig.

Results

1. Estrogen Receptor α

Alignment of the genomic sequence for ERα and published mRNA sequences for ERα show the gene consists of 14 exons and covers 446,296 bp of genomic sequence (Figure 7, Table 3).

2. Estrogen Receptor β

Alignment of the genomic sequence for ERβ and published mRNA sequences for ERβ show the gene consists of 17 exons and covers 253,748 bp of genomic sequence (figure 2, table 1). By analysis with the Celera Genome Browser, we were able to identify a gene, human synaptic nuclei expressed gene 2 (syne-2, accession number NM_015180.1), that is completely contained within intron 9 of ERβ, on the opposite strand. Further analysis of the syne-2 gene showed it consists of 21 exons, and covers 51,471 bp of genomic sequence.

Discussion

Alignment of the complete ERα genomic sequence and various ERβ transcripts shows that the gene covers 446,296 bp of genomic sequence and consists of 14 exons. The alignment of the published sequence for exon 1E (AJ002561) (20) and the ER α genomic sequence revealed that exon 1E actually consists of two separate exons. The newly delineated exon is referred to here as exon 1G to conform to the naming convention previously established. Exon 1G is located approximately 45 kb upstream of exon 1E and conforms to the GT/AG splice site consensus sequence (Figure 1, table 1).

Alignment of the various ERβ transcripts to the complete ERβ genomic sequence reveals a more complex organization than was previously accepted (13). The 5' UTR of the ERβcx variant (AB006589) actually consists of seven untranslated exons (referred to here as exons –1 through –7), all of which conform to the GT/AG splice site consensus sequence (figure 2, table 1). Sequence alignment of ERβ variants AF061055 and AF061054 (12) showed that these transcripts both contain intron sequence and were probably partially mature transcripts. Both of these partially mature transcripts contain exon 7 and a portion of exon 9,

but do not conform to the splice site consensus sequence at the sites where intron sequence is present.

By examining the ER genomic sequences using the Celera Genome Browser, we were able to identify a separate gene contained entirely within intron 9 of ERβ. This gene was identified as human synaptic nuclei expressed gene 2 (syne-2) and was shown to cover over 50 Kb of genomic sequence and consist of 21 exons, all of which conform to the GT/AG splice site consensus sequence (Table 4). The syne-2 gene is located on the antisense strand of ERβ.

Completion of the sequence and structures for ERα and ERβ should contribute to further understanding and characterization of these important receptors.

Table 3: Exon-Intron Boundaries and Locations in the Human Estrogen Receptor: Exon sequences are shown in upper case and intron sequences are shown in lower case. Splice sites are shown in bold.

Gene	Exon no.	Splice varient	Contig start	Contig end	5' splice donor	3' splice acceptor	Exon Size (bp)	Intron size (Kb)
ER1	1G	AJ002561	18941	19032	-	ACCAAAGAAGgtaagttttt	91	33.79
	1F	AJ002562	52818	52940	-	TTCTCTTCAAgtaggtactc	122	11.21
	1E	AJ002561	64150	64280	aaaacaaaagGAAGAAGAAA	CATCACTGAGgtatgtgtga	130	101.95
	1D	AJ002560	166228	166322	-	GAGAGAGCCAgtaagtcacg	94	1.68
	1C	X62462	168002	168120	-	ATCCAGCAGGgtaggcttgt	118	1.55
	1B	AJ002559	169674	169825	-	GACAAGTAAAgtaaagttca	151	0.04
	1A	X03635	169867	170678	-	CATTCTACAGgtacccgcgc	811	34.23
	2	X03635	204912	205102	ttcccccagGCCAAATTCA	AGTATTCAAGgtaatagtgt	190	37.87
	3	X03635	242970	243086	cttttaatagGACATAACGA	ATGAAAGGTGgtaggtacat	116	63.08
	4	X03635	306168	306503	gtgttttcagGGATACGAAA	AGGGTGCCAGgtaagaatgc	335	67.14
	5	X03635	373640	373778	ttgttttcagGCTTTGTGGA	TCTTGGACAGgtaagtgacc	138	49.19
	6	X03635	422964	423097	gttttcatagGAACCAGGGA	CTTAATTCTGgtgagttgat	133	33.26
	7	X03635	456354	456537	gcgcattcagGAGTGTACAC	GGCACATGAGgtgaggcatc	183	4.16
	8	X03635	460701	465237	ccacctacagTAACAAAGGC	-	4536	-
ER2	-7	AB006589	49552	49750	-	GGTTCTGAAGgtgcgtggtt	198	1.18
	-6	AB006589	50928	51235	tgcctcttagACATCCAAGT	TGTTTGTAAGgtaataaaaa	307	32.62
	-5	AB006589	83858	84041	tatccactagAGGGAGACAT	GAGAACACAGgtgaacttca	183	1.90
	-4	AB006589	85942	86154	ctctccatagAAATCCTGGG	ATTAGCCCTGgtaaggagct	212	2.88
	-3	AB006589	89037	89130	cattcaacagTATCTGGGCT	GTGCAGGTAGgtaggtaaag	93	0.67
	-2	AB006589	89803	89988	ccttttacagGGTTTTGTTT	GTGTTGACAGgtaagatgag	185	3.12
	-1	AF060555	93111	93488	-	TATCTGCAAGgtaagcgccc	377	10.96
	1	AF060555	104446	104897	ttctttacagCCATTATACT	CTGTAAACAGgtaagtccag	451	2.47
	2	AF060555	107368	107540	tgctccctagAGAGACACTG	AGCATTCAAGgtacaagaga	172	11.07
	3	AF060555	118610	118726	tctgctatagGACATAATGA	GTGAAGTGTGgtgagtgctt	116	8.05
	4	AF060555	126774	127073	tcctcttcagGCTCCCGGAG	AAGATTCCCGgtagggcttt	299	3.09
	5	AF060555	130158	130296	ctttccccagGCTTTGTGGA	TTCTGGACAGgtgagaaaaa	138	7.56
	6	AF060555	137853	137986	acttttgtagGGATGAGGGG	CTCAATTCCAgtaagtaatc	133	14.39
	7	AF060555	152379	152559	ctttgtccagGTATGTACCC	GGCATGCGAGgtacgcgccc	180	1.65
	8	X99101	154206	154500	gtccccatagTAACAAGGGC	-	826	5.42
	9	AB006589	159915	160827	tctacttaagGGCAGAAAAG	-	912	141.65
	10	AF060555	302474	303300	gtcttgacagCTCTCTCTCA	-	826	-

Table 4: Exon-Intron Boundaries and Locations in the Human Synaptic Nuclei Expressed Gene 2. Exon sequences are shown in upper case and intron sequences are shown in lower case. Splice sites are shown in bold.

Gene	Exon no.	Splice varient	Contig start	Contig end	5' splice donor	3' splice acceptor	Exon Size (bp)	Intron size (Kb)
Syne-2	1	NM_015180	212563	212391	–	CACTGTAGAGgtaaactcac	172	2.22
	2	NM_015180	210175	210044	tttcaaatagACCTGGGACC	GCTGATTAAGgtattgaaat	131	8.94
	3	NM_015180	201109	200946	ttaaatgcagGAACTAGAAC	CTGCTTAAGGgtaagtcagc	163	1.97
	4	NM_015180	198981	198819	tcatttgcagGTGGCCATAC	GTTACAGAAGgtaagggagg	162	1.36
	5	NM_015180	197462	197290	cctttgccagGACTGCATGG	TCGGATCAAGgtaagaaatg	172	12.56
	6	NM_015180	184732	184564	atatgtgtagGGTGAAGAAG	TGAGCAGCAGgtgggacaat	168	5.79
	7	NM_015180	178777	178584	gtaatcacagGATCTACAGC	GGCGCATGAAgtaagaacta	193	0.48
	8	NM_015180	178101	177949	ctcccatcagAATCGAGGAG	GAGGTTTGAGgtaaacacct	152	0.36
	9	NM_015180	177591	177405	tgtgatgcagGCCTTTCAGC	GAGACTCAGGgtgagctcct	186	1.84
	10	NM_015180	175570	175429	acttttgcagCATTTCACCA	CCAACTGAATgtgagggctg	141	0.71
	11	NM_015180	174718	174522	ctctcaacagGGCTTCCAAC	CTGCACTCCGgtacgggcac	196	1.19
	12	NM_015180	173337	173051	tgtggtttagGGCTTGGAAG	GCACTGTCAGgtaacagctg	286	1.76
	13	NM_015180	171289	171140	ttcgtttcagGTAAATCCAT	ACCACCCTATgtaagtctta	149	2.00
	14	NM_015180	169139	169013	ctcattctagGGAAAGCTAC	CAGCAGTCAGgtactgcctg	126	0.69
	15	NM_015180	168327	168117	ttaattccagGTGCCTTCGA	GAGACTGCAGgtgagttaga	210	1.02
	16	NM_015180	167096	166890	tctctggtagGAGATACTGA	GCAGTGCCAGgtacgctgac	206	0.93
	17	NM_015180	165957	165825	gtttttaagGACTTCCACC	GGAACTAATGgtaagtttcc	132	1.48
	18	NM_015180	164342	164149	ctgttttcagCAACTGGAAA	GGGAACCCAGgtgagtctac	193	1.08
	19	NM_015180	163074	162982	tgaatttcagAACCCAGCCT	CCGAGCAAAGgtaagaagcc	92	0.45
	20	NM_015180	162537	162482	ctttacccagCAGTTCAGAG	CAGAGAGCAGgtaacggggc	55	0.27
	21	NM_015180	162214	161092	ctgttggcagGGTCCCCGGC	–	1122	-

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All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the field of molecular biology or related fields are intended to be within the scope of the following claims.

Claims

That which is claimed is:

1. An isolated peptide consisting of an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of a variant estrogen receptor protein provided in Figure 2;

(b) a fragment of the amino acid sequence of a variant estrogen receptor protein provided in Figure 2, wherein the fragment comprises at least 10 contiguous amino acids.

2. An isolated peptide comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of a variant estrogen receptor protein provided in Figure 2;

(b) a fragment of the amino acid sequence of a variant estrogen receptor protein provided in Figure 2, wherein the fragment comprises at least 10 contiguous amino acids.

3. An isolated antibody that selectively binds to a peptide of claim 1.

4. An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes the amino acid sequence of a variant estrogen receptor protein provided in Figure 2;

(b) a nucleotide sequence that encodes a fragment of the amino acid sequence of a variant estrogen receptor protein provided in Figure 2; and

(c) a nucleic acid molecule that is the complement of a nucleic acid molecule of (a)-(b).

5. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes the amino acid sequence of a variant estrogen receptor protein provided in Figure 2;

(b) a nucleotide sequence that encodes a fragment of the amino acid sequence of a variant estrogen receptor protein provided in Figure 2; and

(c) a nucleic acid molecule that is the complement of a nucleic acid molecule of (a)-(b).

6. A nucleic acid vector comprising the nucleic acid sequences of claim 4.

7. A nucleic acid vector comprising the nucleic acid sequences of claim 5.

8. A host cell containing the vector of claim 6.

9. A host cell containing the vector of claim 7.

10. A method for producing any of the peptides of claim 1 comprising introducing a nucleotide sequence encoding any of the peptide sequences in (a)-(b) into a host cell, and culturing the host cell under conditions in which the proteins are expressed from the nucleic acid.

11. A method for producing any of the peptides of claim 2 comprising introducing a nucleotide sequence encoding any of the peptide sequences in (a)-(b) into a host cell, and culturing the host cell under conditions in which the proteins are expressed from the nucleic acid.

12. A method for detecting the presence of any of the peptides of claim 1 in a sample, said method comprising contacting said sample with an agent that specifically allows detection of the presence of the peptide in the sample and then detecting the presence of the peptide.

13. A kit comprising reagents used for the method of claim 12, wherein the reagents comprise an agent that specifically binds to said peptide.

14. A method for detecting the presence of a nucleic acid sequence of claim 4 in a sample, the method comprising contacting the sample with an oligonucleotide that hybridizes to

the nucleic acid sequences under stringent conditions and determining whether the oligonucleotide binds to the nucleic acid sequence in the sample.

15. A kit comprising reagents used for the method of claim 14, wherein the reagents comprise a compound that hybridizes under stringent conditions to any of the nucleic acid molecules.

16. A method for identifying an agent that binds to any of the peptides of claim 1, said method comprising contacting the peptide with an agent and assaying the contacted mixture to determine whether a complex is formed with the agent bound to the peptide.

17. A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor comprising the step of analyzing nucleic acid molecules isolated from said individual for alterations in the estrogen receptor gene sequence, wherein an alteration in said estrogen receptor gene selected from the group consisting of the variants provided in Figure 2 and Figure 4 identifies an individual as having or at risk of developing said bone disorder.

(SEQ ID NO: 1):
Figure 1: Human Genomic DNA for estrogen receptor alpha.

CTGTTGCTTCACCTCAGAATCTTGGGAGAAGCAGGCTCAACAATGAGGGAATCATCCATGACACCCACTG
TCCCAATGACCATCTTTGCCTCCACCTGTTTGTGCCCTTTCACAATCATCAAGATATTGTGATCTTGATT
TCGATTCTTTTGGATACATATCCTGAAGTGGGAAGGCTGGGTTACATGGTAATAAGAGATATCAGCACTT
CCATGTTTATAGCAGCACTATTCACAGTGGCCAAGATATGAAATACGGTATATGCATACAATGGAGTATT
ATGCAGCCATGAAAAAGAAGGATATTCTGCTTCTTCTATCATATGGCATGACATTGATGGACCTTTAGGA
CATTATCCTAAATGAAATAAGCCGGTCAAAGAAAGACAAATACTGCATGATTCCACTTATATAAGATATC
TGAAATAGTCACATTCATAGAATCAAAGAGAGAAATGGTGGTTTTCAGGGGCTGGAGGCAAAGGGAAACA
GGGGAGTTACTAAGAAATGGGCATAATGTTCCAGTTAAACAAGTTGAATAAGCTCAGAGATTTGATATAC
AACATTCTACCTAGAGGTGACAATGTACGGTGCACTTAAAAATTTGTTAAGGGGGTAGATCTCATGTTAA
ATGTTCTTACCACATTAAGAGAAAACAAACAAACAAAAGATACTGTAGTGTTGGAGAATTCTCACAATGG
CTGAACTGGTCTCCACTGAGCCTGGTGGCAAAAGCAGACGGGGGAGGCTCCTCTCTCAGATCAGTTTTGT
AGAGTTGAGGGAGGGGCACCTTGAATGAACATAATACTTGGAGAGAGTGTTGCAGTTAGAGGACAGAAAA
CAAAAGCACATCATCAAGAGTGCCTCCTGCTATGTTTATGCCTATTTTACTGTCCTTTTCAAAGAAAAGC
TTTAAGTTTAATTGATCAACAATTTTTGAATTTTTCTTTTAGTTGTGTTTTCAAATTTATTGATTTCTGC
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ACAGCCTTTTCAGCATAATTCAATGCTTATAACACTGTCTACATATTGTTTTTAAAATGGTTTTGAAGAT
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GTTATGGGGGAATAATATTCCATTGTATGGATATACTACATTTAAAAAATCTATTTGTTATTGGTAAACA
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CAAAAGTTTTAATTTTGATGAAGTCTAAATTATCATTATTCTTTGTTTTGTTGTTTGTACTTTTGGTGTC
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TATTTCCTTTCTTCTGCTGGGGTTGGGTTGGGTTTGTTCTTGTTTCTCTAGTTCCTTGAGATGTGACCTT
AGAATGTCAGTTTGTGTTCTTTCAGTCTTTTTGATGTGGATGTTTAGGGATATGAACTTTCCTCTTAGCA
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TTAGTAGTTGTTTTATAAATTTGGGAGCTCCAGTGTTAGATGCATATATATTTTCCTGATGGACAAGGTC
TTTTACCATTATATACTATCCCTCTTTGTCTTTTTTAACTGCTGTTGCTTTAAAGTTTGTTTTGTCTGAT
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AAGTTTATGTGAGTCCTTATGTGTTAGGTGAGTCTCTTGAAGGCAACAGATAGTTGGTTGGTGAATTCTT
ATCCATTCTGCAGTTCTGTATCTTTTAAGTGGAGCATTGAGGCCATTTACATTCAATGTTAGTATTGAAA
TGTGAGGTACCATTGCATTCATCATGCTCTTTGTTGACTGTGTACCTTGGTTTTTTGTTTTTAAATTGCA
TTTTTATTTTATAGGTCCTGTGTTATGCTTTAAAGAGGTTTCTGTTTTGATGTGTTTCCAGGAATTGTTT
CAAGATTTAGGGCTCCTTTTAGCAGTTCTTGTAGTGGTGGCTTGGTAGTGGCAAATTCTCTCATCATTTG
TTTGTCTGAGAAAGACTGTATCTTTCCTTCATATGTGATGCTTAGTTTCACTGGATACAAAATTCTTGGC
TGATAATTGTTTTGTTTGAGGAAGCTAAAGATAGGGCCCCAATCCCTTCTAGTTTGTAGGGTTTCTGCTG
AGAGATATATCTGCTGTTAATCTGATAGGTTTTCCTGTATAGATTACCTGGTGCTTTTGTCTCACAGCTC
TTAAGATTATTTCCTTTGTCTTAACTTTAGATAACCTGATGACAATGTGCCTAGGTGATGGTCTTTTTGC
AATGAATTTCCCAGTTGTTCTTTGTGCTTCTTGTATTTGCATGTCTAGGTCTGTAGCAAGGCTGGGGAAG
TTTTCCTCTATTATTCCCCCAAATATGTTTTCCAAACTTTTAGAATTCTCTTCTTCCTCAGGAACATCAA
TTATTCTTAGGTTTGGTCATTCAACATAATCTCAGACTTCTTGGAGGCTTTGTTAATATTTTCTTATTCT
GTTTCCTTTGTCTTTGTTGGATTGGGTTAATTTGAAGACCTTGTCTTTGAACTCTGAATTTCTTTCTTCT
ACTGTTCAATTCTATTGCTGAGACTTTCCAGAGCATTTTACATTTCTATAAGTGTGTCCAGTGTTTCCTG
CAGTTTTGATTGTTTTTTCTTTATGCTATCTATTTCCTTGATTATTTCTCCCTTCGCTTCTTCTATTGTT
TTTTGGATTTCCTTGCACTGGGGTTTGGCTTTCTCTGGTGCCTCTGATTAGCTGAATAACTAGCCTTCTG

FIGURE 1, page 2 of 93

AACTCTTTTTTCAGGTAAATCAGGGATTTCTTCTCAGTTTAGATCCATTGCTGGTGAGCTAGTATGATTT
TTTTGGGGGTGTTAAAGAGCCTTGTTTTGTCATATTATCAGATTTGGTTTTCTGGTTCCTTCTCATTTGG
GTAGCCTCTGTCAGAGGGAAGTTCTATGGCTGAAGGCTGTTGTTCGTATTCTTTTATCCCACGAGGTGTT
CCCTTGATGTAGTACTCTCTCCCTTTTCCTATGGATGTGGCTTCTTGAGAGCCGAACTGTAGTAATGGTT
ATCTCTCTTCCAGGTCTAGCCACTCAGCAAGTCTACCAGGCTGTGAGCTGGTATTGCGGGTTGTTGGCAC
TGAGTTCTGTGGTGTGAACTGTCTGTGTGTCTCTCCGCCATGGACACCTGCACCTGTTATGGGGGAGGTG
GTAGAGGGGTGAAACGGATCCCTGGTTCTTAGCTTTGGTGGTTTAATGCTCTATTTTTGTGCTGGTTGGC
CTTCTGCCGGGAGGTGGCGCTTTGCAGACAGCATCAGCTATGGTAGTGTGGAGAGGGACTGGCAGTGGGC
GGGGTCCTAGAGCTCCCAAGAATATATGCCCTTTGTCTTCAGCTACTAGGGAGGGTAGGGAAGGACCATC
AGGTGGGGGCAGGGCTAGGCCTGATCTGAGCTCAGACCCTCCTTGGATAGGTCTTGCTGTGGCTGCTGTG
AGGGGATGGGAGTGAGGTTCCCAGGTCAATGGAATTGTGTACCTAGGAGGATTACGGCTCCCTCTGCGGA
GTCATGCAGGTTGTCAGGGAAGTGGGAGAAAGCCAACAGTCACCAGCCTCACCCAGCTCCTGCGCAATCC
AAAGGGGTGGTCTCACGCCCACTGTGTCCCCGCTAACAACTCTGAGTCTGTTTCCAGGCAGGGGGTAAGC
AGGGCTGAGAACTTGCCGCAGTCTGCCCACCTCCCAGTGGCAAAAGAAAAGGGCTTTAGTTCTTCCCCAG
CCTGTGGAGTCTGCACGCAGGATTCGCACCCTCCCCCGTGTTATGGCCAGGAGGCTTCTTGACCGGTTCA
AATTGTTACAAAGTTCAGCTGGAGACTTCCTTCTTCCTGTGGTGTTTCCCCCGTGCCTCTGGCCACCCTC
CTGAAGGATCCTTGTGATGCCAGGCAGGAGTGGCCTGCTTGGGGACCCAGCGAGCTCCCCAGGCCTTTCC
AGCTGCTTCCTCTATCCCTGTGTTTTGCTTGTCTATCTAAATTGACTCAGCTCCAGATAAGGTCAGAATC
TTCTCCTGCAAACTAGAACTTCAGTTTCCCCATAGGAGGTGTGCGTTCCAGGGCGGAGGATCTCCCTTTC
CCACTTCCGCAGTTGGGGCACTCACATAATTTGGGGTGTCTCCTGGGTCCAGCAGGAGCAGTCCGCTTCC
TTCAGAGGGTCTGTGGGTCCTCCTGGGATTCCTGGTTTATTCCTGCAGTTGTTCTGGAGCTGAAATTCAC
AATGTGAGCCTCTGCACGCTGTTCTGTGCGTCCGAGTCGAAGCTGCCATCTAGTTTTGCCTCCCATCCGT
GGTGATGATCTATGATCTCTACAAGGATACATTTGCTAGAAATATTTGTTCTCTCTGGCCGGGCGCGGTG
GCTCACGCTTGTAATCCCAGCATTTTGGGAGGCCGAGGCAGGTGGATCACGAGGTCAGGAGATCGAGACC
ATCTTGGCTAACACGGTGAAACCCCGTCTCTACTAAAAAATATAAAAAATTAGCTGGGCGTGGTGGCGGG
CGCCTGTAGTCCCAGCTACTCAGGAGGCTGAGGCAGGAGAATGGCGTGAACCCGGGAGGCGGAGTTTGCA
GTGAGCCGAGATCGCGCCACTGCACTCCAGCCTGCGCAACAGAGCGAGACTCTGTCTCAAAAAAAAAAAA
AAAAAAAAAAAGAAATATTTGTTCTCCCTACCCTAAAAGGGATATAATTGAAATACAAAAAAACAATATG
GAGAGGTAATTTCTTTCTTTCTTTTTCTTTTTCTTTTTTTTTTCTTTTTGGAGACAGGGTCTTGTTCTGT
TGCCCAGGCTGAATGCAGTGGGACAATCACAGCTCACTGCAGCCTTGACCTCCTGGGCTCAAATGATCCT
CCCACCTTAGCTTCCTGAGTAGCTGGGACTACAGATACGCACCACCACACCAGCTAAGGTTTAAAATTGT
TTTTAATAGTGAGAGAATTTCACAATTTTGCCAGGCTGGTCTCGAACTCCTGGGCTCAAGCAATCTGCCC
ACCTCGGCCTCCCAAAGTGCTGGGATTATAGGCATGAACCACTGCACCGGAACCTTGGAGAGGTAATTTT
TAACAAGGCCATCTTTTCTCTAACAGAGGAGCACTAAGAAGTCAGATTTCATCCTGGCATGTGACTGTCA
CACAAGCAAATGACTGTGCTGATTAGAAAGCTTGTGTAGCTCAGAAATATCACATAATATGCAGTCTCCG
TTGAGCAACATTGCAGCTTATGTTCATTAGGTAAAACCATAGTAATCTGAAAATATTTTAGGTATATCTG
CCATTATTTTATGACTAAACAAGGAGATGATTTTAGTATTGATTACTTTCATGCACATATTTTAAAAACT
CCTGATTTTTTATGTTGGAAACATTCCAGTTCTTTTTTTTTTTTTTTTTTTTTTTTTGAGACCGGAGTCT
CGCTCTGTCGCCCAGGCTGGAGTGCAGTGGCGGGATCTCGGCTCACTGCAAGCTCCGCCTCCCGGGTTCA
CGCCATTCTCCTGCCTCAGCCTCCCCAGTTCTTTTCTTATCTAGCTATTTTGAACTATACATTTGATTGT
ATTCCAAAAATACGTACAACTATTATGTATCAATAAAATGTCCTAACTTTTTTGCATAGTGAAAGGTTTG
TTCAGGTTATAGTATGAGTTGCAGTCATCCTGTTTTTGGCATGGGAGGGAGATGTTTCTAAACTAGCCAG
TTATAGGTGTCACCTACCAATGTTCTACAAAATGTGGACCAGGCAGAGAGAATTACAGATGCTGGGTGGA
AACTTTGGTTCTGGGCCTGATTCTGCCCCTAACTTGGCGTGAAGCCTCAGTTTCTTCTTACTACAGCAGG
AAAAATAATACTTGCTTTATCTGTTTCATGTGTCTGCTATGATGATAACAAATATAATGTATATGAGACA
ATTTAAAAACTTAAAGCATTTTAAGTTCCTTGGTCTTTATGGGAGAGGGAGGACCATCATTTCTTTCTCT
TTTTTCTTTTTCTTCTTCTCCTCCCCTTTCCTCCTCTTTTTTTCATTCCTTCTTTTTCTCCTTATCTTTC
TCCTCCTCCCTCTCCTCCTTCTTCTTCCTCCTCCAACCTCCTCCTTCTCCTCGCTTCTTCCCTTCTACTT
TTACTTCCTTCTTTTCTCCTTCTCCTCCATTCTCTTTCTCCTCCTCCTTCATCCACTCCTTCTTCTTCTT
CCTTTTGAGATGGAATCTTGCTCTGTCACCCAGGCTGGAGTGCAGTGGCATGATCTTGGCTCACTGCAGC
CTCCACCTCCCAGATTCAAGTGATTCTCGTGCCTCAGCCTCCCTAGTAGCTGGGATTACAGGTGTATGCC
ACCACACCCAGCTAATTTTTTTTTTTTTTTTTTTTTTTTTTGAGACACTATTTCACTCTTGTCACCCAGAC
TGGAGTGCAGTGGTGTGATCTTGGCTCACTGCAAACTCCACCTCCCAGATTCAAGCAATTCCCCTGCCTC
AGCCTCCTGAGTAGCTGGGATTACAGGTGTGCACCACCATGTCTGGCTAATTTTGTATTTTTAGTAGAGA
TGGGGTTTCCCCATGTTGGCCAGGCTGGTCTTGAACTCCTGACCTCAAGTGATCCACCTGCCTCGGCCTC
CCAAAGTACTGGGATTACAGGTGTGAGTCACCGCACCCGGTCCTTTCCTTCTTCTTCCTCTTCTTCTTCT
TCTTCCTTCTTTTCTCTGTCTCCTTCTCCTTTTTTTCCTCCTTGTCCTTCTTCTGTCTGATGCATAGTCA
AGGGTTTGATAAGTGTCTGCTCTGTGCTGACAGTTTCAGGAGCAGTACAGAAACTCCTATTTTGTACTCC
AAATAATCCACAAGAATTAATTGGATCACCTCGAAGGAGGAAAGAGAAGCTCAAAGAGATCAGGTAAGTT
GCACAAGCTCTGAATCCCAGCACACCGTGAAAACGGGCTTCAAATCTGGTCTTTCTGATTCCAAAGTCTA
TAGTCTTACCTGTGATTCACTTTCCTGATTTGTTAAAAAAAAAAAAAAAAAAAAAAAAGGATGCTTCATTTG
CTTAAGTAAAATTCCAGGGAATTTTCAGCAGAAGTTTTAAATGTTGGTAGAGAATTTTCTTGAGGCAAAA
CTGATAATCATAAAGCTTGTCTGGCTACCAAAATTGATCTGGTAGTCAAAACTTCTTGGTAAAGTTATCA
GTATAGAGACCCAAGAGAAACAAATAAGAAGAATCTGCTACTAAATTTTGGCGGAGTTGAGAAATTTTTT
AATTTGAGCTTTCACTCTAAGAGATAAGAGTCTGTGACCAATTGTATTGTGTGTTTTGCATTGCTATGAA
GGAATGCCTGAGGCTGGGTAGTTTATAAAGAAAAGAGGTGTATTTGGCTCAGAGTTCTGCAGCCTATACA
AGCAGGGCAGCAGCTTCTGCTTGGCTTCTGGGGAGGCTTCAGGAAGCTTTTGCTCATGGCAGAAGGCAAA
GAGGGAGCAGGCATGTCACATGAGAGGGAGCAAGAGTGGGGGAGGAGGTGCCAGGCTCCTTTAAGCAACC
AGCTCTTGCATGAACTAATAGAGTGAGAACTGAATCATTACCATGAGGAGGACACCAACTCATTCATGAG
AGATCCGCCCCCATGACCCAAACACCTCCCACCAGGCCCCACCTCCAACACTGGGGATGACATGTCAACA
CAAGATTTGGACGGGACAAATATTCCAACTATTCACCCATGTTCCCTAACTTGAAGGGAGTTCACATTAG
GACAAGTTCACTGAAATCTTTGTTTTGGAATGGGGATGGATAAGACATCATTTATTAAGTTATGGTTTTT

FIGURE 1, page 3 of 93

AGTTTCTGGCTTTGGCTAACTCAAACAAAAAGGGAATATTTCAGACTGGTGCTTGGTAAATCATAGAATG
ACAAACAATTGGAAGACCAGGTTAAAATGAACTTGGAGGACATTAAGTGAATTAAGCCAGGCACAGAAAG
ACAAATACTGCAAATTCTCACTTATATGTGGAATCTAAAAAAAGTTGAGCTTATACAAACAGAGAGTAGA
ATGGTGGTCACCAGAGGCTGGGGAAGGAGGAGTTGAGGAGATATCGGTCAAAGCATACAAAATTTCAGTT
AGGCAGGAGGAATAAATTCAAGAGATCTATTGTACAACATGGTGACTGTAGTTAATAACATTGTGACTGT
ATTGAATTCTTGAAAGTTGCTAAGAGAGTAGATTTTAAGTGTTCTCACTTAAAAAAATAAGTATGTGAGA
TAATGCGTATGTTAGTTAGCTCTATTTAGCCATTTCACAATGTGTATGTAGTCCAAAATCATGTTGTACA
TGATTCATAAATACATTTTTATTTGTCAATTAAAAATACCCTGGAATTTGGGCAACAAAAGCTATCTGCC
CAGGTGGGAACAAATCGCCTCTGAGCATCTTTCCTTCATTGCATCTCTAATCAAGATAGAAAGTCCCTGG
AGAGAGGGTCTGATTGGACAAGCTTGAGTCCGATCCCTATACTTTGGCTATGAGAGGAATATTCTTGCTG
AAGTCGTCTGTGATAGACCCTGTGGATGCATTTGGCTTGGAAATACGAAAGCGCCTTGATTTAGAATCCC
CTCAAGTCTGTCTGTTCACAGTGGGATAATTTTTATTCTCTTCCTCTCCAGAAGGAATCAAGGGGTGTCA
TAAAGGAGGTATGTCTGCTAAGCAGAACTACCTCCCCTCCCCAAAGAAAGTCTGTTACCATGTATACTTT
TAAACATTTTATTTTAAAATAAAATTAGACTCACAAGAAGTTACAAAAACAGTACAGAATTGCCATGTAA
CTTTTACCCAGCTCCCCACAATGATACCATCTTATATAACTCTAGTACATTATTAAAATATGGACATTGA
CACCGGTAAAATACTATTAACAGAACCACATACTTTATTCTGCTTTTGCTTTTTATTTTATTTTATTATT
TTATTATTTTTTGAGACAGAATCTCGCTCTGTCACCCAAGCTGGAGTGCAGTGGTGCCATTGCAACCTCT
ACCTCCTGGGTTCAAGCAATTCTCCTATCTCAGCCTCCCATGTAGCTGGGATTATAGGTGCCCACCACCA
TGCCTGGCTGATTTCTGTATTTTTAGTAGAGATGGGGTGTCACCATGTTGGCCAGGCTGGTCTCGAACGC
CTGACCTCAAGTGATCTGCCCGCCTCTGCCTCCCAAAGTGCTAGGATTACAGGTGTGAGACACCACGCCC
AGCCTGTTTGGCATTTTTTTAATACGTGCTCTATAATATTGATTTTTGTGTAAACATGTGTTTGTATATA
TCTATAACGAGAACTCAAGTCATACTGTAATCCTATTTTGTAAACTGACTTTTTTCCTTTATCAGTATAT
CAAGATTATTTTCCCACATCATTTGACATTTTTTCTACAGTGTAATTTAATGGCTACATTGTTTTCTATC
CTATGAATATATCAAACCTATTTCTTAAAAACCCTACTCAGGGATTTTAAAAAATAAAAACGATGTTTTA
ATATTATAAAGATTCAGTGAGGTATATTCTTATACGTACACATTTCTAAGGTTTGAGTTCTTACAAGATG
CTGAACTAGCTAAGACTACTGGTTCTCATCTGTCACATAGGGAAAAATTATAGAAGGAAAACATCAAGAT
TTGGAAAAATCTGTGAGAATTGTTTTGCATTAGTGTGTAGGTGTGTGTGTTGGGGTGGTGGCTGCAGCTT
GGGGCAGAGGCCTCAGGTGTGGCTGTGGAGTGATCAGATAGAGTTTTTGGAGTTCGGCTTTTGCCCCAGG
ACACTTGGTGCCTGCCCCCAGAGCTGCAGCCCAGAAGGCCGTTCTCAGAGGTGAAGTCCAGGCAGTGAGG
AGCTGTCTGCCAGTAGGCAGTTGAAGAAAAAAAATGAGCTAGAGGAAAAAAACAAAAAAACAAAATCTCC
TTCTAATGCTGCCAGGCTGCCGGGAGCTGGAAATGAAGCACTGACAGGAGTGGGTATTTCATGGTGAAGG
GAATAATCAACTGGTTTTTTTGGTACCCAAGACTTTCCACCTTCACACACACACATGAGATGCTTTGAAA
TAAAGATAGTCACTTGACTTAGTAAAGTTTGTTGACATAAAAATATGAGAAATACCAAAGAATACAAAAA
GGAAAACTTCGTTAATATTATTCAGACTTAAAATTCCAGATTGTATCAACATTAAGGGGGTTGATGAAAA
CATGGGAGAAAGCCAAGGGACGTGAGATCGGGCTCAATTCTTGACTTGCTGGGGGAAGGTATCAACACAG
AACTTTTAAGAATTAGAAGGCATTAAAAAGAAATAGAAATCCTGAATCAAATTGAAACAGTAAAATAAAA
TAGTCCAAAGATGTGTAAATATATCACTATCACAATAACTATAAATAGGTTAAATTTGCCAGTTGAAAGA
AAGGAACTATTAAATGAGATTTTAAAAATTTGGATATATGCTTTTCATGTGAACATACCTAAAGCATATA
CACAAAACCAGAAAATAAAAAGATGGAAATATCCACAGAGTGACAAAGGAAAGCTGGTGCATTTGTATTA
GTATCAGATAAAGCTCACATTTAGATAAAAAACATTATAGTAATAGAGAAAGTCACAAGGTTAAAGTTTC
AATTCACCAAGAAATATCCATTCTAAACATGTATACATACCCAATTAAGCTGCCTCAAAATATATATGAC
AAAAATTGGGAGAACTATAAAGTCAGATATAAGGATTGAAAAGAAAGAAATGAAACTAATTATTTTCAGA
TGATATACACGTTTACATGAAAAAACTCCAAAGAATCTTCAGGCAAATTATTAGAAATTGTAGGAGAGCT
CCGCAAGAGGGCTGGATATAAAATTAATATACAAAAGTCAATGTCATTTCACTATACCAGAAAAAAGACA
ATAACATTAGAAAATAAATCTAACATAAGATGTAGAAAAACTTCTTAGAGGAAAAATTTTCTTGGGAAAT
ATTAAAGAAGATCTAAATAAGTAGAATTACATAATATTCATGCATAAGAAGGCAACATTTTGAAGACGTC
TTGTTATACATAGGCCTAGGAATAATATAGTTTTAAGCTATATTATTTTGAACTGTAGATGAAGAAAAGC
TCTTTTTTTCCTTGAGTATTTTAAGATTTTGAATAAAGTCATATTGCTCTAGGAATATTTTATACTTCTG
CCAGCAGTGTTTGAGAATGCCTACTTCCTACATTATCACCACCATAAATGTTTAAAACCTGATAGCACAC
AGTTTAAAAAATTTGTAATTCTCCAATTAACAGTGACCTTTAAAAATTATGTTTACTGATCTCTATTATT
TTGTCCTTTGTAAATCTTTTATTAGTTTTTATGTTCACATGTTCCGTTTTAAAATAGACTTTTAAGAGCT
CTTTGTATTAAGAATATTAAGGCTTTGTCCATATAATTAGTATTTTTCAGAATACCCTTTCTAGGTACAG
TTTTTCAGTTCCAGTGCACAGAATGGAAACTTGCTACCTGCTACACCACATTTTCACTAGTATGTGATGT
ATTCATCACAAACAACAGTATTGGCCAACATTTTCCCTCACTGTGAAGTGCACATTTGACATCCTTTAGA
AAAATTACTGACGGTTTTGAGACGATTGTTCTGTGCTTTCTTTCAGTCAGCATAATTTTCCCGAAAGCAG
AGATGACTCTTCCAGACTTGCTACCAATGCTTGAACAAACTGTGTAAGCTTAGTCCAAAAAAAATATTTG
ATTAATAGATTTTATTTTGGTAGATTCTAAGGTTCCAAGCAGTCAGAGAAATAATCGCAGAGCCTCAAAT
ATCTCCAAAATCTGATACCAATCCTTTTGATTGTGAATTATATTCTGTAGCTACCAAAGAAGGTAAGTTT
TTATTTTTTCTACTCTATTAACTTTCCCTTGGACAACTGAATATTAAGATGACTATGTAAGGAGGTTATC
AGACCAAGGCCTCACACATCAGGATAAAAGCACATGCCATAGAAAGAACATTTGTGTCTCAAAAGGTGAT
ACCAAGACAAGGCTGTGGGATATATATGGGCACAATGGTTGATACCTTCAAAGACTTCATACATGGTGTG
GAGGTTTTTGGAGATTTTAATTTATAATGACAATCTTTCCAGTTAGGAGAATTTTTGGACTGTAAAGTTA
GCCAAACAACTTTTCAATGATAATAAATGTCTATATCTTACACAGGGGGAATACAGTTTTTGTTTGTTTT
AGTTTTTTCTCTGTCTATTCATATAGGGGCATCATATGTCTTTATCATTAAAAACTGATTTAGATAGGCA
GTTGTAGAGAAATTTAATGTGTGGGAATTTAAAGTTTTAAAAAGATGTAGCAAAATATAGATACATTTAA
GACCCACTGCACCAATGAAAAAGGGAAATTAATTAAACTAGACAACTTTTATGGGTACTAACCATTAAAA
TTAAAATTTTAGTCATTGTAAATTACATTACATTATAATAGTTTTCAATCTATTGTTAAGTTAAATATTT
TGGGTAACAATTGTATTTCACAGTTGTTCACACTTTGCATAATTTTCTAAGGAAAATGAGTCCCTTAGGG
AGAAAATTGTTCTTAAATTTTATTGTTGGATAATGTTGCTGTACTAACATGGTTTACTGAAGTGGATCTA
CCATGGGTGTTTAGGTTTTTGTTCTTTACAAAATGTATTGGGTGAAATTTTCCATATCACTGGTGAACTT
TTCATGCTAATTTTCCAGTCCCTTAGTTTAAATATTATGCATTTTTTCCTGCAAATCTATCTTGAATCTG
AAAAGGCCCCAGAAGGAATTAGCGTGAGTCCAGAGTAGATGGACTGCAAATGTTACACATATTTCAATAT

FIGURE 1, page 4 of 93

GTATCCAGCTTTCAAAAATAGCTTATTGAAATCAAGGTTGAACCACATGAAATTTTGGGTTTTTTTGGAT
GTAAAAAATGGTTATATATTGGCATTTTCATATCATCCAATCTAATATCTTCCTCTAGTGAGGTTCTGGC
AAAAAAAAAGTATGATGACCAGAGTTGTTCACTCTTTTAAGCTTTATGTTTCAAAATATTTTTAAAATTT
AAAACCATCTAAGTGCATCCCAAAAAACATTGGAAAATTTTGTAGGCTAGTTTTGTTTAATGATTTTTCT
TCTATAGATTTATTTTTATGCTATGCCTTACTCTCCAATTAGATTTTAGCCATCCAAGAAAGGTACCTTG
TACTTCTAAGCGATTCTCCCATCACCTGGACGTTAACTGCAGCCCACACTGCAGTGTCTTGACTGCAGTA
GGCACTCAGTAAATATTTATTGATGGTCCTGATTATGGGATGATGAAATATGCTAAAGGTAACTTAAACT
TTTGTCAATAAAAACCGAGTTTCAGGTTAGTTTGACCTTTTCCGTATCTCTAAATATTTTCTTTCATGTCA
TTTTTGTGAAATAGCTCACGAAAGTACTTATTGATTCTGAAATCCTTTTCCCCTCTGGTATTCCTGAGCT
ATCCTCACTCACACACAGCACACCAGTGCTATTGTTTGCTGTTTTGTTAAAATCATTCTCATTAATATTC
CTCATTCAATAAAAAATAGTTGATTCCCACTTATGCACCAAACTCTATTCTAAAGACTGCTGTTTATTTTA
TGGAGTCAATATCATCATTTTGTTTTCCATTCCACATAATAGTTGGATGCCAATATGAAGTGTATATTTA
TAAATAATATGTGCTTTTTTTATTTGTTTATTTTTATTTTACTTTAAGTTCTGGGATTAATATGTGCTTT
TAACATTATTGTTTAAAAATAACAGGAGATATCATATCTTAAGCACCTTCTATATTCTGGGCACTGTTCT
AAATGTATCAAAGTTATCATCTCATTTAATCCCTCCACACACCTGAGGGAAGAGAGTATTATTCCTTATT
TACAGATAAGGAAGCTGAGGCTTGGAAGATTCATATATCTAAGATCACAAAGCTAGTAAAGCAGCCAAGT
TTGAGTCTAAATCCAGGTTTAAATATCATATTGCATGTGGGCATAGATGAGCAAGAACAGGTTTTCCTG
AAGATGGCCAGTCTAAGGCTTAGAAGAAGGAAGCTCGGGGAGCCTAAACCAAGATATGCTAAGGCAAGTT
TTTTTGCTCGTTTGTTTTTGAGATGGAGTTTCGATCTTGTTGCCCAGGCTGGAGTGCAGTAGTGTGATCT
CGGCTCACCGCAACCTCCGCCTCCTGGGTTCAAGTGATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGAT
TACAGTCATGTGCCACCATGCCCAGCTAATTTTGTATTTTTAGTAGAGATGGTGTTTCACTATGTTAGCC
AGGCTGGTGTCAAACTCCTGACCTCAGGTGATCCGCCCACCTCAGCCTCCCAGAGTGCTGGGATTACAGG
CGTGAGCCACTGTGCCCGGCCTGCTAAGGCAAGTATTGACCATTAGAGGAGATGACTAGTCCCAGTGGCA
GGCCTTTCCTACTGGGAGTCAGCCAAGAGCTCCCCACTCTTCTGGTTCCATTGTTCCTCCTGCAAAGTTC
CATTCATAAAGTGGTTTCCCATTTGATTGTCCAATGATGCAAATCTCCAGTCCTTTTTAGCACTGAGTTT
CTCATAGCCTTTTACCATTGAGTTTCTCATGGCTAATGAATGCTAATGAATTGGCATTCCGATTTATCTA
TAGGATTCCATGAGTCAGCCTCATGAAAGAAGGTTCCACTCCCTCACTGTGGGTACCGTCTGGGAATTAG
ACCCTTAATAGGAGTAATTCAGCAGGCAATGTCTTCTCTAATAACACTCCAGTCTCACTGAGAGCTTCTA
TTCAAAACAACAATCTAAAGGTCTACAGTGTGACTTTCAACTAAACTGAAAAAAGAATAGAAAATGAATG
TATGTGATGTACACATTCATTCAAATGTTTATCCCTAAAATTCATAGCAGATTATGACTGATCATTAAAG
CCAAATTAAGGGGGCAAAATGTATAAAAACAAAAGGAACTCTTAGGCATAATAGTCTTTAAAGTAAAACA
TTACTACTGACAGTTGCTTGTGTGAAAGATATCTTTATTTAATATGGTAAAAAGAACACAGGAATTGCTA
GCACTTACCGTATGTCCATTTTATGTCCACCTTAAAATAGATATGTCTGTATAGTCATCAGATTAGCACT
TTAGAATTCAATAATTTCAAAGAAATCAGAATGGACATTCATTACATGTGCTTATCTGGCAGGAGAATTG
AACAAATCCTTTCTATAGGAAAATGTAAAATTCCTAATAACTCCACAGGATTGTAAGACTTGGGCTGGTA
ACTTCAGTGAATACAGCAGAGTTTGGGCGATGGGAAAAGGTACAGTTGTGTTCCTAAACTCTTAACTTTG
TGAGGCAGTGACTTTATTTCTTCTTCATGATTTTGCAGTAAGTTCAGTACAGTGGTTAGTTTCAGTATAG
TTCAGTGGCTAAGCTTTTGAGAGGGACAGTTCTATGTTCTAACTCAACTTCTGCCACTTGTTAGAAAGTG
ACTCTTGTCAAACTATTGGCCCTTTCAAACCTCAGTTTCTTCATCTGCAAAACTTTATTCATGGGGTTGT
TGTGAGGGTTAAATGAAAAATATGTAAAACTCATCAAAATTTTAAGCACAAAATACCAAGTCTCAGCAGA
ACACATACAGTAGGAGTCCAGCCATTAAAATTTGAAACAGGCAGAGGCAAAAATATTTTGTTTAGAAGTA
CTTGCATTTTCTAGCTCTTTGGCTGAGTGGACAACATTTTGGTGTTCTTTTTCTTATTGTTATTTTTTAA
AGCATACGTATATGTTATGTAGACTCTTTTGTATGTATATTTAACTCACAATAAATATTTATAAATAGAA
AGAAAGATATCACATATATGTGCACATACACTGGTAAGCCCCAATACACTGCCTCATTTCTAAATGACTC
TAGCATTTGTAGGACAGTGCTTTTAAACCTTTCGCACTCACGAGATACTCTGGGGAGCTTTAAAATATAT
GCTGATGCTTGGGCTCCACTTCCACATATTCTGATTTAATTGATTAGGGGTTCGGCTCAGGCATCAGTAT
TTGTAAATAAAAGCTTCCCAGCTGATTCTAATGTGAAGTTAAAATTGACGGATACTGATACCGATAAAAG
AGTGAGTGCAATAGACACAAAACAAAATAGGAGATGTGTCTCAACAATGGTAAGATTGTTTTAAAAATTA
TAGTACAATTAAAAAAATAATGTAATGCAATTATTTAGAAAATTCTTACAATTTTGTATTTTGAAAGCAC
CATGTGGATATCATGGGGAAAACCAGAACTTTGTTGGATTTCCTTAACAAAGATTTTGCAGCTTGGTATC
ATTTCCATTTTGTAGTATTTTGATATCCAGGAGATGAAAGTGGGAAGTGGACAATTGCCTATAAGGCCAT
GCTTTGCACCAGGGTGTCCAGATGAGAGGCAAGTGGAGGGTAAAGTTTAGCCTGCATTCTGTTCCCTAAG
GTACATCTCCTGGTGAGGGGTGGCTTCTAATCAGGGGAAGAAGTCCTATGTCTTGTTTCCTAATGCACGC
ACAGGTTCCACAAGCCCTCACTTTGTTCTCAAGAGCATAGCATTTATTTGGTGCTTAAGACTGCTGAAT
GTCACAAAATAATTTTTCCCAGCACAAACAAATATTCAAAATAGTTATGTGCACAGCCTGTTTGAGCACC
AATAAGTTTTGGCTCTGTGGCCTGTTTGGGCACTGACATGGTTTGGCTCTGTGTCCCTACCCAAATCTTA
TCTTGAATTGTGATCCCCACATGTCCAGGGAGCGACCTGATGGGAAGTGATTGGATCATGGGTGCAGTTT
CTCCCATGCTGTTCTCATGACAGAGAGTAAGTTCTCAGGAGAGCTGATGGTTTAAAAGTCTTTGGCAGTT
TCCCTTTCTCTCCCTCTCTCTCCTGCTGCTATGTAAGACGTGCCTTGTTTCCCCTTTGCCTTCCGCCATG
ATTGTTTTAAGTTTCCTGAGGCCTTCCCAGCCATGTGGAAATATGAGTCAATTAAACCTCTTTTCTTTAT
AAATTACCAAGTCTCAGGCACCTAAACCAATTAGAAGGTGTGCCATTGGCACACAGCAGGGTCCTGGTGT
CTCCCCCACCATCCAGCCACCACTCTGCCAGGTGTGAATGTATTAACTATTGCTGGAGTGAGGTGAAAGG
AGGCAGTCCTGCAGAAGGGCCACTGCCACTGGGATGGCACAGGAGGGCGCTCGAGAGACTCACCTTAGTG
ACTCTATCAACTGGTGAAAATATTTAGATATTTTCACAATCAATATGGCCTTGCTTGTATATACAGGGTG
ATTATAAACTCTCTTGCCACTTATCACAGAAGTCGAAGTTTCATCATTTCTTTTCCTGTATTTGGTTTAT
GTGCAACAATATAGGTTTATTTTCCAGTTCTGGAAAATAATCATGGTTAATACTGACTGAGAACTGATCA
TTTCCTTTCCTCTTTATACCAACCAATGGGGCAGGTACCATTATTAAAGGGGGAGGAAATAGAGGTTAAA
TAACATGCCCCCAATCAGTAGTGGGGAAATGAAAGAATCAGGATTCAAAGCCAGGTTTGTCTGGGTCTTG
GGACCAGCTCAGCGTCTGTGCTGTACTGCCCGGGACTCCTGCTGCCAATTCTTTCTACCTCATTATCCCT
CAACCCTGCACCAGCAAATCCACAGGGCGTGAGATGAAGAGAAGAGAGGACCACAGGCGAGAAAGTGGCA
GCAGCAAGAGAAGATGTACCATGAGGAAGTTCTGGGAGGTTCTGCCCGTCTTTCTGAGAACAGGGGAGAG
ACAGAGCTGAGTTACAACTGCACTGCTTCTTAGCTTCTTAGTTTCTCTTCAGAATTAGTGGCAAAGAAGA

FIGURE 1, page 5 of 93

GTTTTCGAAGTCTTTAGCATGTATTAAACGAAGAATTTTGTTTATAAGAAAAAATTGTGGATCGTTCCCA
TGTTTGTCTGGAAAACTCTTGTTAAACTTTTGTGCAGCTAGTAAATTAAGTCACTGTTTATTCTGTGTAG
TGGAAAGCATGCTTAAACTCTAACTCAGGAGACCTGATTCCAGGAATAGTTAAGCCTGAGTTCATTATAA
ACCACTTAAGTTATCTGTGTCATTATTCTAGTCTGTTAAATGGAGGGCTTGAGCTGGTTTCTTGTAAGGT
GGGATTTGGCTAAGTGCTCTTGGATACAGTTGCTCACCTCTTTGAGCCTCAGCTTTCTTTTTGGTGATTA
TTTAATCGCATGTGATAACAAATACAGGGTGTTTTGTGTAATGCCTGGAATGGCACTGAGATTGTCTCCA
CTACAGTAAGGAGGTGGTTTAGAAATTAGCTAATTTATTAATTAATGGCCTATAGAGCTTCATGTAGGTT
GGTACTTCAAAGTCCCATTCATATGGATCATGTTCATATTTATATATTCATCACTTTTATTTCAAAATCT
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TGAAGTGCTATTATTTGGTATCGGCTTCCTTTGGTGGTGTTGGTTTTTGATTCCCTCTGCCCCGGACTCT
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AAAAACTATCATGGAAGAAATAACTAAGAAATAACCATTTAAAATATATCAGGATATAATGAGGATGAAG
CTTTAGATAACACAAAAAGGCAATTTCTCTTTAGGCTGAAAAATACCAGACACAGATATATCGACAGAGT
GACCTGCCAGAATCCCTACTTTCCAGCCCATCTGATAAAGGTCAACGATTGAACACCCAAACACGTTGAT
ACACACAGCACCTGCCTGATGAAAACCGTTAACAGTGTTTTTCTCAGCCCAGAGTGCACTGTTTTCTTAA
AGTTTTGAAAACAGTAATCTAAATTTCCCTATTCCATGAGTAAAGTTCTACTTTTTTCTTTTTCACACTA
AACAGCATTCGATGTTTTAGCTGAAAGTCAATTAAGAAAAATGTATTGTGTCTGTGTTTTTCTTGCTTTC
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CGGTAACTCTCATCATAATTTTATTATTATGACAAGTTGGGTTTATGAAGTATTTTTCCAATTACTGCCT
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GAACTCAGAAGCCCAGAACTCCAAAGCTGGAAGCCACCAGATCCTAGCAAGTGAAGCTCTGTCAATCTGG
AGCCGCAGATTTTGACCACGTGTGCACAGCCTCCCATCTGGGCAAGCCCTTTTCTCTCCACCACTCCACT
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CCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCAGGGAACATATAGTTGGCAGCAAGGGTTGCAGAAC
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GGAACTTAAGATTTAACTCAAGAAGACAGGGATGTTGCTTGCAAAGACCCTGAAGATCTTGTCATCCAAA
CTGTGACTGCCTGGAGACTGTTTATACAGGATCTTGAACTGGGCTAGGAGAGTGCAATGGATGGTAGTCC
CAGTCCTTGTTTGCAGGGAGAGGAAGACAGCGACAAAGCATTTCTATGGAAAGAAGGAGTTGCTCATAAG
TCTACTATGGACATCAAAATATGCTGATGAGCCACAGCAAGTTCATTACAAAGGGATTTCAGATAGAAGC

FIGURE 1, page 6 of 93

CTCCTCCTTCAGAGTGAGGAGGAAGAATCATCCAGGAAAGAGAGAAATTATGTGTATTTCATATATTGCT
GTATGTACATATTAATCAGCCAGCAAATATTAAGTGCATTCATGGGCAAAATGCCAAAGAGATGAAGAGA
AAAATCAGACTCCAAGGATCATATAATCTGATTGTGGAAGAAAGGCATATTCATCATGAAAATGTAGCAA
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AACAATTTATTTCTCGTGGTTCTGGTGACTAGGAAGTCCAAGATCAAGGCACCAGCAGATTGGTTGTCGG
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CCTCCCAGAGTGCTGGGATTACAGGCGTGAGCCACCATGCCCGCCCTAAACCTTTTTTAAAAATATGTTT
TAACATTCTTTGTGCTCAAATTCATGATCAATTTTTTTTTTTTTTTTTTTTGAGATGGAGTCTCACTCTG

FIGURE 1, page 7 of 93

TCACCCAGGCTGGAGTCCAGTAGCACGATCTCGGCTCACTGCAAGCTCTGCCTCCCGGGTTCACGCCATT
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TAGGGTGTCCGGTTTTTCTTGGCGGAGTAAACATCCACCCAGTAGTATTCACTCAGTTTGCATTGTTCTG
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FIGURE 1, page 10 of 93

CTGCTTCATTTAAATTGTTGTTTTCTTCTTTTTTAATTGTTCAACCTAATTGTCTAATAGTGATGAATGC
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TCCTGGGCTTTTTTTGGTTGGTAGGCTATTAATTCCTGCCTCAATTTCAGAACTTGTTATTGGTCTGTTC
AGGGATTTGACTTCTTCCTGGTTTAGTCTTGGGAGGGCGTATGTGTCCAGGAATTTATCCATTTCTTCTG
GATTTTCTAGTTTATTTGCGCAGAGGTGTTTATAGTATTCTCTGATGGTAGTTTGTATTTCTGTGGGATT
GCTGGTGATATTCCCTTTATCATATTTAGTGTGTCTATTTGATTTTTCTCTTTTCTTCTTTATTAGTCT
GGCTAGCAGTCTATCTATTTTGTTAATCTTTTCAAAAAACCAGCTCCTGTGTTCATTGATTTTTTTTGA
AGTTTATTTTGTGTCTCTGTCTCCTTCAGTTCTGCTCTGATCTTAGTTATTTCTTGTCTTCTGCTAGCTT
TTGAATGTGTTTGCTCTTGCTTCTCTAGTTCTTTTAATTGTGATGTTAGGGTGTCAGTTTGAGATCTTTC
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TTCTGGTATGTTCTGTCTTTGTTCTCATTGGTTTCAAAGAACTTATTTATTTCTGCCTTAATTCTGTCAT
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AATCCTGAGTTCTAATTTGATTGCAGTGTGGTCTGAGAGACTGTTAGGATTTCCATTCTTTTGCATTTGC
TGAGGAGTGTTTTACTTCTAATTATGTGGTCAATTTTAGAATAAGTGTGATGTGGTGCTAAGAAGAATGT
ATGTTCTCTTGGTTTGGGGTGGAGACTTCTATAGATGTCTATTAGGTCTGCTTGGTCCAGAGGTGAGTTC
AAGTCCTGAATATCCTTGTTAATTTTCTGTCTCATTGATCTGTTTAATATTGACAGTGGGGTGTTAAAGT
CTCCCGCTATTATTGTGTGAGAATCTAAGTCTCTTTGTAGGTCTCTAAGAACTTGCTTTATGAATCTGGG
TGCTGCTGTATTGGGTGCATATATATTTAGGATAGTTAGCTCTTCTCGTTGCATTGATACCTTTACCATT
ATGTAATGCCCTTCTTTGTCTTTTTTGATCTTTGTTGGTTTAAAGTCTGTTTTATCAGAGACTAGGACTG
CAACCCCTGCTTTTTTTTTGCTCTCCATTTGCTTGGTAAATCTTCCGCCATTCCTTTATTTTGAGCCTAT
GTGTATCTTCTGCATGTGATATGGGTCTCCTGAATACAGCACACCAATGGGTCTTGACTCTTTATCCAGT
TTGCCAGTCTGTGTCTTTTAACTGGGGCATTTAACCTGTTTACATTTAAGATTAATATTTTTATGTGTGA
ATTTGATCCTGTCATTATGATGCTAGCTGGTTATTTTGCCCATTAGTTGATGCAGTTTCTCGTAGTGTTG
ATGGTCTTTACAATTTGGTATGTTTTTGCAGTGGTTGGTACCAGTTTTACCTTTCCATATTTAGTGTTTC
TTTTAGGAGCTCTTGTAAGGCAGGCCTGGTGGTGAGAAAATCTCTCAGCATTTGCTTGTCTGTAAAGGAT
CTTATTTCTCTTTCACTTATGAAGCTTAGTTTGGCTGGATATGAAATTCTAGGTTAAAAATTCTTTTCTT
TAAGAATGTTGAATATTGGCCCCCACTCTCTTCTGGCTTGCAAGGTTTCTGCAGAGTGATCCACTGTTAG
TCTGATGGGCTTCCCTTTGTGGGTAACACGACCTTTCTCTCTGGCTGCACTTAACATTTTTTCCTTCATT
TCAACCTTGGTGAATCTGACAATTATGTGTCTTGGGGTTGCTCTTCTCGAGAGTATCTTTGTGATGTTCT
CTGTATTTCCTGAATTTGAATGTTGGCCTGTCTTGCTAGGTTGGGGAAGTTCTCCTGGATAATATCCTGA
AAAGTGTTTTCCAACTTGGTTCCATTCTTTCTGTCACTTTCAGGTACATCATCAAATATAGGTTTGGTCT
TTTCACATAGTCCCATATTTCTTGGAGGCTTTGTTCATTCCTTTTCACTCTTTCTTCTCTAATCTTGTCT
TCATGCTTTATTTCAAGTTGATCTTCAATCTCTGATATCCTTTCTTTTGCTTGATTGATTCAGCTATTGA
TACTTGTGTATGCTTCATAAAGTTCTTGTGCTGTGTTTCTCAGCTCCATCAGGTCATTTATGTTCTGCTC
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AGAACATGCTTCTTCAGCTCAGAGGAGTTTGTTATTACTCACCTTCTGAAGCCGGCTTCTGTCAATTCAT
CAAACTCATTCTCCATCCAATTTTGTTCCCTTGCTGGCAAGGAGTTGTGATCCTTTGGAGGAGAAGAGGT
GTTTTGGTTTTTGGAATTGTCAGCCTTTTTGTACTGGTTTATTCTCATCTTCATGGATTTATCTACCTTT
GGTCTTTGATGTTGGTGACCTTTGGATGGGGTTTCTGTGTGGATGTCCTTTTTGTTGATATTAATGCTAT
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ACCAAGCTTGAGCATCCCAGGTCAAGTTCTGACTGCTGTGCTGGCAGCGAGAATTTCAAGCTCATGGATC
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GAAAAGTGTAGTATCTGGGCAGGAGTGCACCGTTCCTTAGGGCACAGTCCCTCAGGGCTTCCCTTGGCTA
GGGGAGGGAGTTCCCTGACCCCTTGGGATTCCCAGGTGAGGCGATGCCCCACCCTGCTTTGGCTCACCCT
CTGTGGGCTGCACCCACTGTCTAACCAGTCCCAATGAGATGAGCTGGGTACCTCAGTTGGAAATGCAGAA
ATCACCTGTCTTCTGCGTTAATCTCACTGGGAGCTGCAGACTGGAGCTGTTCCTATTTGGCCATCTTGCC
CCTTGGTCTGGTTTTCAACCTTCAGTCTTCCATATTTATTTTGAATGAATTTTCTGCAGCTTTATTAAAA
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TGATTTGACAGCTTTGTGATAGTATCTTGTAATCCAAGTACATGATATATTTCTACATTATTTAGATCTT
GTGTTAGGTTTTTCCATAAGATTAATTTTCTTCATATTGGCTTTCTTGCTATGTTTCTTTTTAGCATAAA
GCTAATCCAGGAAAAGGAATAAAACTGGAAGGAAAAAAATGTCTTAAACCATTAATATTGGCTGACCCCGG
TGGTAGGGTTATGAATGAAACATTTTTGCTTCTTCCACTTTTTTATATTTTCCAAATTGTCCATATTAAT
CATGTATGATTTTTATAATAATAAATTAATGAAATTTAAGAATTAGATAATTGATTGAATTGGATAATTG
AATTAATAAAATTTAAGAATGAGAATAGGAATAATTGTGCTTTGAAAAGTCATATACACAAGAGTTTTAG
ATGGAATTCAATACTAAATTTATATGCTATACTAAATCAGTAATTCTCAAGGAGCAAAGGTGCTGGGGAG
TGTGGAGGAGCTCTTTGTTGGTGTTGCACATACAATTTAAGACAACATTTTCCTTATTCCTCACCATTTT
AACCATATCACCTAACCAGCCTCTGGTAGCACTCAATAGACATCTGATGAATGAATGAATAAGTGAATGA
AAACATTGTGACAAAATGGTATAACATTTTGTATTTGAAAAATATATGAAAATCTATTCTTTTCAAATAT
AAAATGGGAAAATAAAATTCAATAAAAATATCTTGGTTGGTGAGAATACACAAAAGATATACCTTCTTGT

FIGURE 1, page 16 of 93

CTATGAATTAGTAATAAGAAATTGTCTTGAGGAAGTCAACTACATCTGGAAGGTTCTCTCTGGACAAGGA
GCATAAGTGAAAAACAGTGCACTAAATTATAACCAAGAGTTGCAACTTACCATTTTAATGCTTCAGCACA
GGCACAGAGACTAACATTTACTAAGCAAACAAGAAGTCTTGGCAAGTTAATTAAATAATGAATTATTTTT
GGTGACCAAGGAGTTGGGCTTCTCATTTTAAAACCATGCATGAGATTTTTCCCTTTCTACCCATTACTAA
AATATCGTATTAGTGTGAAAAATTATACCAGGACTGGGAGAAAAAGAAATCACATCTGTCCTTGACAATG
GGCTGAATGAAGAGGTGAAGGAGTGGTTTTACTATCTAAGTGACTGAAAAATAGGTTATGGTGCCCCAGC
AAATCCTTGTTGTTTGCTGACAATTAGTGATGTCTGTTTAAATCATGCAGTTTTATTAGGCCTTAAAAAT
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CGGTTGGAAGCCTTCAACTTTGTTCTCCCTGTTTTCAGATGAGTGTCTATTTGTGGCTCTACCTTTTCTC
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GGCAGTGGGAGAAACACCCTAAATCAGTTGGAGGTGAGGAAAGAAGAAAAGCACCCCTATCTTGGTAGTT
CCTCATTCTTCCCTTCGTCACGTCCATGTCATCAGGCTCTGCCTTCATCTGCGATCTGGATACAATCCAA
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TCCATCAGTAAACAACCTAGACTAACATCTTGCCGTTGTTTACATCTCGTGGTGTAGAGTTTACACCTTG
TGGTCTAGAATTTACATCTTGTGGTGGAGGCAGGCAGATGATTAACAATAAACTTAAGTAGGTCTAGATG
TCAAAAGGTGGTAAATGCTACAGGAAAGAGCAAAGGTCGAGCCAGGTAAGGCAGATTGGCTGTGTGGGTG
TGGAGGAAGGGTGCAAGAGTACTGTCAAGATAAGCCTTCCTGAGAACATCTGAACCAGGACATGAAGGAC
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GTGAAAACTTAATTGGCGAGCAGATTAATATGGTGATCTTCCCTTAGATCACTAGGAAAATCTTGTTTTA
TGAATTTTTCTTCCCTTTTCATTCACTAGCAGAGAAAAGAGTTGTAAAGGAGCCGCAGAAAATTATAGTA
GGTTTCTCCCTACTACTGAGCTACTGAGACTGGAAGATGCTCACGTTAGCAACTGAGTATATTTATGTAT
TTCCCTTTAATGTTTGAAGGGTCAGGAATATTTGACTTAGGATACTAGTCTGTTTAGAAACATGATTCAA
CTAGCTACATGACTAAACTAGCAGCTGTCAGAGAGAATGCAAGGTCAAAACTTAGTAGTTGATAATAATA
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CTGGCAATATGCTGAGTGTTCTACCTCTAGCATTTTATTCAAACTGTGCAATCTGCCTGCTGAAACAAGT
ATCATTAACTTCATTTCCTAAGGTGAGAAAATTGAGGCCCAGAGAGGTTAAATAAGTTTAGGATCATATG
CATAGCTGGTAAGTACTATACTTTAATATCCCTTTGCCTTCATGCTTTGCTCTCACTCCATGTTTAAATG
AGCAGAGAGACTTATCTTTAAACAGATATATAGCAAGTAGTATTTTCCAAATGAATTCCACAAGATGCTC
CATTGCAAAAGTTCAAATAAGTTTAGAAAAATGCTGCAAACTTTGTGCTTCTTAAGAGATTTACAGTGCA
GATTAGCACATTAAAGCCTTTGGGAAATTTGTATTAGAAAAACCTTTATTAACTTATTTACCCCAATTTT
TCCAAGCTTTTTGATCACGAAACTCTTTAAAAAACAACAAGTATAATTGCTTTTATAGTATTCTTTGGGA
TACACTTGGAGAAGTGTTACATGAAAAGATATGATTGGATAAATTTAAATATAGGAAGAATTATTTAATC
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GACATAATTTACTTTTGTCCTTGTAAGGACATAATGCACTTTTAGTGGTTTGCATTGTTTATTTTCTTTT
GAATTTCATGTTACTTTATAAAGGTAATTATTTAATCAAACCATTTGTTAAGTGTCAGACACTATGGTAG
GTGCTGGTAATATAAAGAGAATATGTAAACATCAACACAACATATCTCCTAGTATGGGCTTACAGTACAG
TGAGAGACACAAACAAATAATTTGTAGGATTGAAATAAGTCTTACATTTGCCACATCAATAAAGCACTAT
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GGCTACTAAGACAGAAATAACAAAAATCAGATGTGGGTTTAGAAAGAGCATTTTGGCTGTAATACAGAAC
ATGATGGATAATTGATGGAGCGAGATTCCTGGGGAGATAGAAGAGGATAGGGCCATGTAAGTACATCTGC
TGGTATTTTAAAATTAGAAAAAGAAATTTTTGGTAGCAAAATCAGAACAGACCCACCAACTCTTTGCAAA
TCATGGGACTAGAATGTTTGGAAAGGAAGATGCTAACGATTTTCATTCATTTGTTTATCATCTATGTTGA
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TCCCCACCTCTCCTTTCCAGAAATTCAGTATATCAGACTAATTGGTTTACAGTTGTGACCATGGGCTTTT
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GGCTTGTGCTTCAGCACTGATTGTGTGCACCGATGGTGGAACATACCTGCCTGCTCAGAAGCTTTGGCTT
CTCTCTGTAGGTGAGAGACAGCCATTAGAAGTCCTTGAACAGGGAAGAAACACGGTGAAAGCAAGGATTT
CATTGAGAAGTCCCTCATGGAAGAAGAAGATTACATTGGAAAGAGCCTGGCTTAGGGAGGGAGCAGTGAC
AATCAGAGAAAAAGGCAGATAGGGGCAAAGATACTGGAAGAAGAGGAAAAACTGTCCAAAGCTTTGTCCT
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CTCCAAAACCATTGTCTTTCCTTAAAACAGTAATGATCACAAGCAGCTTACAACTTTGCATATAGCCACT
GGGGCAAAATCCTATTAAAAGCTAATTCATTATCTGAGCCAGTGCATGATAATGCGATGTAAAGGCGTGT
TGGGAGGCAGATGATCAGAACTTTTAAGCAAACTAAATTTCATAACATTTATTAGAAGCCTGTCTCTATT
TCCAGAAAACGCCTATAAATGTGGCTGTAATGTAGGCTACAGGTCATCACACTGAAGTAGAAGCAATGTA
CAATACCTGAAAGGTTAGAGAAGTTCAGGGTCTGGGCTTATAAAAAACTTCATTATTCATTTGAAAGATA
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AAATGACCACAAAGACCTGTCCTCACAAGTGGGAGCTATTAATCAATAGTGTGTACACATGGACATAGAG
AGCAGAATAATAAACACTGGAGACTCTGAGGGGTGGGAGGGGAAGAGGGAGGTGAGGGATGAGAAATTAC

FIGURE 1, page 17 of 93

TTGATGGGTACAATCTACACTATTCTGGTGATTGATTTCTCTCTGTTTCCTCTTCAGAAACTGAGAGGAA
ATTTAGTTTCCTCAGTCACCACTCCTCCAAACTCCTGCGTGGGTGATACAAGACTTGCTGTCATCTTGAG
GCAGAAGGGGTTAGGGGATTTCCCCATTGAACCTGATAGCCTTCATTTCATTTCTGTCTTCTCAGGGAAA
CATTTACCCCTCTTTACTAAATGGAAGAAGGTTTGTAAACTAGGAGGGTATCTATGGATCTGATTGCTCC
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ATCCCAGCACTTTGGGAGGCCGAGGTGGTCGGATCACCTGAGGTCAGGAGTTCGAGACCAGTCTGGCCAA
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TAGCTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGCCGAGGTTGCAGTGAGCCGAGAT
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AGTGCTGGTACCCCCTAAATCTATAAAATTTTCTAAAAAATAAAATGACAATAAAGGAATGAAAAAGGCA
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GAAAGCAGAATTGGTGTAAAGTCTTTAAAAGGAGCAATTAGATCCACAAATACCTTCCTAGTTTCTAATT
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ACACACACACTTACTTCACTTCTGCTGGAGGAATTTACAAGATGAAGAACATCTTGTATCTCTTTTGGGC
TACTGTTTGTGAAAGGAATGGTTGCATGTGCTCTTGGCTAAGCCAACTCCATCCTGAAGACAGATTTTTG
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CTGCTTTTTCATTTTCAGATTTAAATCCAGAGTTATTACAGATGGTAACATCTGATGCCAATTTATGGAT
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GACATTCTATGTATTTTCCTTTGTATTTCAAAGTCAGAGTCAAGTATTTAAAAAGATAAGATCTTTCATT
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CACTAAATATACTTTTAGTGATATTTGTTGATTGGAGCATAGCTTTTGTGTTTGCCAAACATCATTGATG
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TCTTTTGGATTTTCCAAATATACAACATGCCATATATGAGTAGTGACATTTTTATTTCTTCTTCCTAGCT
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TGATGGTGGGCATTCTTTTCTCACTCCTGATCGCAGGGCAGCATTTAACTTTTCACCATTATGAATGATG
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CTGGGATTACAGGTGTGAGCCACTATGCCTGGCTGGATTCATTAATTTTCAAATGCATTTTAAAATTTCT
GAACTAAATCCAACTTGATTATAATATACTATCTTTTTTTAAGGGAAAAGTAGATGAATCAGACTCAGCA
AAAATAGGAGCCAGAATAGCAACTGATACGGTTTGTCTATATTCCCACCCAAATCTCATCTTGAATTGTA
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TACTCACTCTGTCTCTCACCTGCCACCATGTAAGACGTGCCTTGGCTACTCCTTTGCCATCTGCCATAAT
TATCTGAGATCTCCCCAGCCATTTGGAACTGTGAGTCAGTTAAACCTCTTTTCTTTATAAATTACCCAGT
CTCAGGCAGTTCTTCATAGCAGCGTGAAAATTAACTAATACAGCAACCATGGCAGGGGAAGGCCAAGCAC
CTTGACTGAGTATATCCAATGGGAGAGGAGATTTTTTTCTCACAGCCAAATCAGGACACTCACAGCTTTG
TGTTTAAAAGCTTGGGCTCTGGACTCAGGCTGCCTGGTTTGAAGTGCCAGTCCTCCCTCTTATGTGGCAG
GGGACCTTAGCTCTGAGTATCCTTCTCTATAAAGGAGGATGATGTTCTATTTACCCAATAAGATTCTAAG
GATTAAATGATACATTAAAGTGCACAGGTCAGATCACTCTCAGCCCATAGAAGTAATTATAATTCCAGCT

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AAATGTACAGTTTTATAAGTTTTGATGTATGTATACAACCATTAAACCACTACCACAATAACATAAGGAA
CATACCTGCCCCCCATCCACACATTTGATGCGCCTCCTTTTAAAATTCTCTTTCCTACCCTCCACCCCTC
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AAGACAGCAAAAGTGCTTTCTCACTCTGGAGTTCTACTTGATTTTAATGGACATAGATTAGTGTGAACCA
CATAAACCAGTACTAAAATACAGGATTTGATCTAGAAAAGGTGATGCTAAAAATGCATGTAGATAAAACC
TAATTTTTTTCAGACACCAAAATGAAAAATTATTAGTATGCCATGACACATGAACACTTTTATATTCCAC
AACCACTGTGCTCTCCTTTTGGTGTTCATTTGCAATGGATGGAATGTTTATGTCCCTTCCAAATTTGTAT
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GTGGAACCCTCAAGAAAAGGATTAGTGCCCTCAGCAAAGAGGCCTAGGAGAGCTAGCTTGCTCTTCCCAG
CATTTAGGGACACAGCAAGAGGGTGCCGTCTGTGAACTAGAAAGCAGGCCCTCACCAGATACCAAATTTG
CCAATGCCTTGGCCTTGGACTTCCCAGCCTCCAGAACCATGAGAAGTAAATTTCTGTTGTTTATAAGCCA
CCTAGTCTATAGTGTGTTTTGTTTTAGCAGGCTGAATGGACTAAGGCATTATTTATTGTGAGTTCTATTC
ACCATGGAGCATATGTGGCCTATGTGTCCCTGGCACTGAGGCAGGAACTGAGCAGAGTACGCAGGGGAAT
TAATAAATGCTTGGACCTATCTTTAAAACACCTAGAGTTTAGTAGGAATCAACTGGAAGTAGTAGGGTAAA
GGAAAGTAGGTGACTTTTGTTGAGCCCTGCCATGTGCTAGAGACTGTGCTAAAGTGATTTACCCACATTA
TCTTATTTGAACCTCATGGCAAGCCTGTGTGGTAGGTCCTATTCCTCTATTTACAGATGGGGAAACTGAA
GCTCAGAGACATTAAGTAATTTGCCCAAGGTTATAGAATTATCAGCAACAAAGCTGAAAGTGGCAAAGGG
CTCTTTCTAGTCAGGAGGAATTAAGAGAGCTTGGGTGCAGTGGCTCACATCTGTAATCCTAGCATTTTGG
GAGGCCAAGGTGGGAGGATCAGTTGAGCCCAGGAGTTTGAGATCAGCCTGGGCAACATAGTGAGACTTCG
TCTGTACAGAAAAAAAGAAAAAAGAAAAAAAGAGCTTGGGATCGTGCCTCCTGTGACTCAGCATCACCTT
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FIGURE 1, page 19 of 93

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FIGURE 1, page 23 of 93

TATTTTTAGTAGAGGCAAGGTTTCACCGTGTTGACTAGGGTGGTCTCAAACTCCTGGCCTCAAGTGATCC
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FIGURE 1, page 27 of 93

ACCCAGTGACTCAGGTTGTTTTCTTACTCCAAGGATCTCTGTGCAAGTAGGAATCCTGACATCTTCTCTT
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FIGURE 1, page 29 of 93

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FIGURE 1, page 33 of 93

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CTTGACATTTTACCGAGAGCCTTAAATTTTGAATGGTGAATGCTAATGTTCTTTGTGCATAAAGAATTTC
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FIGURE 1, page 40 of 93

AATCAATTGAAGATTAATATAGTAAGTAGCAGAAGAGAAATAAAAAAATCTTCTAGAGAGTTCAGAACAG
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TAGCTCCTTTAACAGCTGTGGCCGGTAAGCAGGCACTTATTTGCTAAAGAACTCAAGCCCATTTAGCTGG
CTTCATCTGCTTTGTAGAGCTCTGTTAAAAAGAGTTCCTATTTCTCCACATCCTCTCCAGCACCTGTTGT
TTCCTGACTTTTTAATGATTGCCATTCTAACTGGTGTGAGATGATATCTCATAGTGGTTTTGATTTGCAT
TTCTCTGATGGCCAGTGATGATGAGCATTTCTTCATGTGTTTTTTGGCTGCATAAATGTCTTCTTTTGAG
AAGTGTCTGTTCATGTCCTTCGCCCACTTTTTGATGGGGTTGTTTGTTTTTTTCTTGTAAATTTGTTTGA
GTTCATTGTAGATTCTGGATATTAGCCCTTTGTCAGATGAGTAGGTTGCGAAAATTTTCTCCCATGTTGT
AGGTTGCCTGTTCACTCTGATGGTAGTTTCTTTTGCTGTGCAGAAGCTCTTTAGTTTAATTAGATCCCAT
TTGTCAATTTTGGCTTTTGTTGCCATTGCTTTTGGTGTTTTGGACATGAAGTCCTTGCCCACGCCTATGT
CCTGAATGGTAATTCCTAGGTTTTCTTCTAGGGTTTTTATGGTTTTAGTTGGTGGGACTGTAAACTAGTT
CAACCATTGTGGAAGTCAGTGTGGCGATTCCTCAGGGATCTAGAACTAGAAATACCATTTGACCCAGCTA
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AAGAAAATGTGGCACATATACACCATGGAATACTATGCAGCCATAAAAAATGATGAGTTCATGTCCTTTG
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CTATGGTCTTGAGTTTACAGCTCTCAGTGTAAATCTTACTCTCAAGAGAAAAATTTTCCTTCTGCAGCTG
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CCCAAAGTCACTTTCTCAGAAGTAGTGTTACCCTTCCACGAGTAATACTACTCTTACTTCTCTTTACAGC
TCTCAAATTCTTATGAAGTTTTCCTATTTATTCATTTGTTTGATTATTGTCTGTCTGCATCAGGTACCGT

FIGURE 1, page 42 of 93

GCAAACTTGGATGTAAACTCAGTGATAGCTGATTTCTGTTCAGCATTGTTGTTGCTATAGCTCCAGTGC
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GCCTTCTCCTTCATCTAAGCCGTTTGCTTATGTCTTTTTTCTTGTTGCGAGACATTCTGCACATTGCCAC
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TAGCCCATGGAATGGTCCTTAAACAAGAGTTCAAGGACTGCCACAATCTTGTTCTAGCCTATCTTTCTAG
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AAATATGATGATTCCATTTCTTTGCTGGGAATTTCTTTCCAGATTTACCTGTAAAAATTCTTCGAACCCT
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AATTTTGTTCTTTTTGCATATCTGTATTTTTATTTTTCCACAGTAAACATCTTTTACTTCTGTAATAAAA
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GACATCAGGTAGCTGAGGCCAATACAATATTATTCCTTTGGGTTGTTGAGAAATCATAGCAGAGGAAAGC
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GCCTAATTGCCCTGTCCAGAACTTCCAACACTATGTTGAATAGGATGGTACTGGTACCAAAACAGAGATA
TAGACCAATGGAACAGAACAGAGCCCTCAGAAATAATACCACACATCTACAACCATCTGATCTTTGACAA
ACGTGACAAAAACAAGAAATGGGGAAAGGATTCCCTATTTAATAAATAGTGCTGGGAAAACTGGCTAGCC
ATATGTAGAAAGCTGAAACTGGATCACTTCCTTACACCTTATACAAAAATTAATTCAAGATGGATTAAAG
ACTTAAATGTTAGAACTAAAACCATAAAAACCCTAGAAGAAAACCTAGGCAATACCATTCAGGACATAGG
CATGGGCAAGGACTTCATGTCTAAAACACCAAAAGCAATGGCAACAAAAGCCAAAATTGACAAATGGGAT
CTAATTAAACTAAAGAGCTTCTGTTCTTTGCTGGGGTATCTGAAGACTGAAAACACAGCAAAAGAAACTA
CCATCAGACTGAACAGGCAACCTACAGAATGGGAGAAAATTTTTGCAATCTACTCATCTGACAAAGGGCT
AATATCCAGAATCTACAAAGAACTCAAACAAATTTACAAGAAAAAAGGAACCCCATCAACAAGTGGGTGA
AGGATATGAACAGACACTTCTCAAAAGAAGACATTTATGCAGCCAACAGACACATGAAAAAATGCTCATC

FIGURE 1, page 45 of 93

ATCATTGGCCATCAGAGAAATGCAAATCAAAACCACAATGAGATACCATCTCACACCAGTTAGAATGGTG
ATCATTAGAAAGTCAGGAAACGACAGGTGCTGGAGAGGATGTGGAGAAATAGGAACACTTTTACACTGTT
GGTGGGACTGTAAACTGGTTCAACCATTGTGGAAGACAGTGTGGCGATTCCTCAGGGATCTACAACTAGA
AATACCATTTGACCCAGCCATCCCATTACTGGGTATATACCCAAAGGATTATAAATCATGCTGCTATAAA
GACACATGCACACGTATGTTTATTGCGGCACTATTCACAATAGCAAAGACTTGGAACCAACCTAAATATC
CAACAACAATAGGCTAGATTAAGAAAATGTGGCACATATACACCATGGAATACTATGCAGCCATAAAAAA
GGATGAGTTCATATACTTTGTAGGGACATGGATGAAGCTGGAAACCATCATTCTCAGCAAACTATTGCAA
GGACAAAAAAACCAAACACTGCATGTTCTCACTCATAGGTGGGAATTGAACAATAAGAACACTTGGACACA
GGGTGGGGAACATTACACACTGGGGCCTGTTGTGGGGTGGGGGGAGGGGGGAGGGATAGCATTAGGAGAT
ATAACTAATGTAAATGATGAGTTAATGGGTGCAGCACACCAACATGGCACATGTATACATATGTAACAAA
CCTGCACATTGTGCACATGTACCCTAGAACTTAAAGTATAATAAAAAATATTTAAAAAATCTACAGTCCC
TTTCTCAATAGGTAAACACTATTAACAATTTCTTCTGAAAATTACATATGTACACACACACACACCCCAC
ACATAGATATTTTGTTAACATACATTACCTTATGCTCTACACATTATTCTGTGCCTAGCTTTTCTCATCG
AATAATGTGTATTGGAGATCTTTCCATATAAGTACATATTGGTCTCACTCATTCATTTTTAATGGCTGTA
TATTAGTCCATAGTATGGAGTAATAATACCTTTTATTGGCACAAAGTTTTGCAGTTGACAAAGGGTTTGC
ATATATTGTTTCATTGGGTTGTATAGCAGTCATCAACGGACATATCAAGAATCCCAGAAGGGTAACCTGG
GCTTCACCCAGGATCGCATGGAGCTTGGGACTCAAACAGCTAACATTCCCTAAACAGGCCCATATTCCTG
CAATTTAGTGCAGCTGCTACAACATTTAGGTAAACTCTTTGAAAGCAGTAAAAAGATCACCAATCTGGGA
CATCAAGAAGCCAGACGACAAGGAGACATAGACCTCAGGTGAGTGAGAAAAGAGAATAATTGAAGTTTAG
AACTGAATGGGCACTAACGAACAACAGATACATCTCTTTCCTTTCACCGATGAGGACCTGGGTGTGGCCT
GTGGATGTTAAGTAGCATGTTTAGGCCACACAGCTGGATTGTTTCTTTCCTGAGGCTAGCTCTGGAGAG
GGGAGGAAACGGAGATGCTAGATTTTTCCGGGCTCTCTTTTCTCATCAGCTAGAATGGGATGTGGATGGA
ATGCAGCTTGAGAAGCCAAACACCCTTGAGAAATGAGAACTCTGCTTTCTGATGTGGGGCGCATCCTATC
TGAGATAACTCTCCTGCCAGCGCAGTATGACCATTGCGACTTGAGCTGTGTGGGTGCCCAGGTGGTGTAG
ACCTTAAAACCACTCCTGCTTTTGTTTACTGAATGTCTAATATTCACACAGTTCTTTGTCTGAGTGCAGG
GCCAAAGCAGCAAATAACGAAGAAGCTGTGCCCAACCATAAGAACTATGAAATGCTCCAGATCATCTACG
CTAGTTTGAGTTAAATTTACCATGCAAATAAATATAGAACATTTCTTCTTATGCATAGATTGTATTTGTT
CTATTAAACAACCATCCTGTAAAGGTTTTATTCATTCATTTATTTTTATTTGTTAGGAGAAATTGTTATT
TAAGCTAAGAAAGTAGACTAGTAGTTATTTCTTTTTTTTTGCTTATTATACTTTACGTTTGGGGATACAT
GTGCAGGTTAGTTACGTAGGTATACACGTGCCATGGTGGTTTGCTGCACCCATCAACCTGTCATCTAAAT
TAGGTATTTCTTCTAATGCTATCCCTTCCCTAGCCCCCCACCCCCTGACAGGCCCCAGTGTGTGATGTTC
CCCTCCCTGTGTCCATGTATTCTCATTGTTCAGCTCCCACTTATGAGCGAGAACATGCAGTGTTTGGTTT
TCTGTTCCTGTGTTAGTTTGCTGAGAATGATGGTTTCCAGCTTCATCCATGTCCCTATAAAGGACATGAT
TGCATCCTTTTTTATGGCTGCATAGTATTCCATGGTGTATATGTGCCACATTTTCTTTATCCAGTCTATC
ATTGATGGGCATTTGGGTTGGTTTCAAGTCTTTGCTATTGTGAATAGTGCTGCAGTAAACATACGTGTGC
GTGTGTTTTTAGAATAGAATGATTTATAATCCTTTGGGTATATACCCAGTAATGGGATGGCTGGGTCAAA
TACTAGAAGGCTACAGTAACCAAAACAGCATGGTACTGGTACCAAAACAGATATCTAGACCACTGGAACA
GATCAGAGGCCTCAGAAATAATGCTACACATGTACAACCCTCTGATCTTTGATAAACCTGACAAAACAAG
CAATGGGGAAAGGATTCCCTATTTAATAAATGGTGTTGGGAAAACTGACTAGCCATATGCAGAAAACTGA
AACTGGACCCCTTCCTTACACCTTATAAGAAAATTAACTCAAGATGGATTAAAGACTTAAATGTAAGACC
TAAAACCATAAAAACCCTAGAAGAAAACCTAGGCAATACAATTCAGGACATAGGCATGGGCAAAGAGTTC
ATGACTAAAATACCAAAAGCAATGGCAACAAAAGCTATAATTGACAAATGGGATCTAATTAAACTAAAGA
ACAACTGCACAGCAAAAGAAACTATCATCAGAGTGAACAGGCAACCTACAGAATGGGAGAAAATTTTTGC
AATCTATCCATCTAACAAAGGGCTAATATCCAGAATGTAGAAGGAACTTCAACAAATTTACACACACACA
CACACACACACACACACAAACAACCCCATCAAAAAGTGGGTGAAGGATATGAACAGACAGTTCTCAAAAG
AAGACATTTACACTGCCAACAACATAAATATGCTGCCAACAAGCATATGAAAAAAAGCTCATCATCACTG
GTCAAGAGAAATGCAAATCAAAACCACAATGACATACTATCTCACACCAGTTAGAATGGCAATCATTAAG
AAGTCAGGAAACAACAGATGCTAGAGAGGATGTGGGGAAATAGGAACGTTTTTACACTGTTGGTGGGAGT
GTAAATTAGTTCAACCATTGTGGAAGACAGTGTGGCGATTCCTCAAGGACCTACAATTAGTAGTTATTTC
TAGGTCTGACGGGCTGTCTTTTAGTTTGTTTTCTTATTCTGAGGTGGACTTAAACCAATTTTAAAAACAG
GGATGACTGAATTCGTGTGTTAATCTTGTACTACAGGAACCCTTTGACATTGATTCAGAAGCACCCAAGT
GTTTGTTCATTAATCCTTTTTTATTTTTGCATATTATTTATTTTTCAACTTTTATTTTAAAAATCAGGGG
TACATATGCAGGTTTGTTACAAAGGTATATTGAGTGATGCTGAGGTCTGGCATATGGATGAATCTGTCAC
TCAGGTAATGAGCATAGTACCCAATGATAGTTTTTTGTACCCAATGATAGTTTTTTGTTTTCTTTGTTTT
TTTTTGTTTGTTTGTTTTTTGAGATGGAGTCTCGCTCTGTCACCCAGGCTAGAGTGCAATGGCTTGATCT
CGGCTCAATGCAACCTCCGCCTCCCAGATTCCAGCAATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGAC
TACAGGCGTACACCACCATGCCCGGCTAATTTTTGTATTTTTAGTAGAGATGGGGTTTACCATATTGGC
CAGGCTGGTTTTGAACTCCTGACCTCAGGTGATCTGCCCACCTCGGCCTCCCAAAGTGGTGGGATTACAG
GCGTCAGCCACTGTGCCTGGCCCCAATAGATAGTTTTTCAGTCCTTGCCCCTGTTCCTCCTTCCCACTTC
TAGTTATCACCAGTGTCTATTGTTTCTGTCTTTATGTTCATGTGTACCAAATATTTAGCTCCCACTTATA
AGTGAGAACACATGGTATTTGGTTTTCTGTTTCTATGTTAGTTTGCTTAGATAGACCTCCAGCTGCATCC
ACGTTGCTGCAAATGACACGATTTCATTCTTTTTTATGGCTGTGTAGTATTCCGTGGTGTAGATATACCA
TATATTCTTTATCTAGGATAACTGATGGGCAATTGGGTTGATTCCATGTCTTTGCTATTTTGAGTAGTGT
TCTGATGACCATATGGGTGCATGTGTCTTTTCAATAGAACAATTTATTTTCATTACTCTTATCAGGATAC
CTGGGAGGAACTTCTCCTACGAAGTTAATTTGGGGGGACTCCTGAAGATGAGTGAAACCCCTTATTAAGC
ACTTAGAGGGTCGAAAGTGTACAAGGGAACGTTCAGGTGTGACAGCTTGAGAGACATGCATATTCCACCC
CCACACCAGAGCTTAGTGAACCGTCTTTTCTATTTCTCCCAAAGCACCAAAATGGCCCAGAAATTGGAA
GATGGAAAATGGACTTATTTATGAGTCTGGGAAGGCAGGGCAGTAAGCACAGTCCTGTTCAGGGTTCTGA
GTTTTACCCTCTTGCTCTGATTGCGAGATCATTTTCCTCTTCCTTGCTTCTTCAGCTTAGGACAAGAACA
GTTTGGAAATTGTTTCTACTACTTTGGACACCATAGTTTAGATTTCAAATGAGTACAAGTGGGAGGAAAG
CTTGGATAATTCTCTGGAAATAATCGAACAGAGTGAAGGAGAGGGGTCTACAGGTGAGCTGAATGCTGCA
TGGCATTGAAGTAATCACACCAGTCGTCACAATTCTCTCCTCTTTGATGGTTATCTGTTGTCCCAGAAGG

FIGURE 1, page 46 of 93

AACAATTTCAGAAAGTCCTTTTCTGGACTGTAGAATAGCACTTGCTTATTTGATGAGCCCTGAGAAGCAT
TACTGAAAGCGGTTCATTGTCCCTGAGGTATTACAATGAGATGGTGGTCACTGATTTCATTATGTTTTCC
TTTATTGCAGCTGTTGGTTTGATCCTTTGCCAGGTGCTTAAAACAATTGTGGTTTTGCAGATGGTAAGTT
AGAGGTTGGACAAAAAAAGGGATCATGTCACTGCCCTGGCCAAAATTTCAACAGACTGGGGTCTAGTGAG
GGCAAATAGATAGAGGCTTTCCTCTTCACTTTGTGTTATTTAGAAAAAGAAACTTTCCAGGACAAATTTC
TTTCCTAGAATTCCTTTTTTAAAAATTTTTTTTCTTTGAAAATTTACTTAGATGCAAATAATATATTTTT
CTTCCTTTTAAATAATAAAAGTAAGATGTCTCTTGGAGGTGGTGGTTGTCACTGACAAGATTAACTAGAA
CTGACTAGCTGTAAAAATATAATTTGGGATGCATTATTAAGGCATGCCATTTTTATTTGCATGCCATTGT
GTACAGATGTGGTTGTGAAATAGTTCAAATCATGGCACATTGAATGTCCTCACTGGATTTTTAGGAATGT
GTTCACTGAGACAGCCAAATCCTATTTCATTTTCTTTGGCTCATTGCATTGGCTGTAAATTGGAGATATT
CACTTTAATATGTGAGTCAAAATTTATTTCCAAACATAATACTGCAGTTGTTCTGTCACAGAATATAAAT
TTCTTATTTATTTCCTTAATACGTTGCTTTCTACTTTTTCTTTTTTTCTTTATTTTATTCTGGAGTATGT
GGAAAGGTTTTCCAGAAAGATTTGCATATGCCATAATCTACTGATGAATACTTTTTTTGGGTTACTCTTT
CATATTTTGGGAGATATAACTATGGAAGTGTTAGGAATCATGGGTTCTGGAAATAGTTTTATTACTGCTT
CTGAAATGCCCTCCCAATGATACCATATAGTAATTCCATCAGGGAATAATATTTTTATTATAGTTTAAAA
TATAACTTAATATTTAGGTGCTCTTGTTCAGTCATCGTCAAGTTCTTTTTATTTCACCAACCCTACCATG
GCACTCCTGAAAGACTTGTGAATGCGACAGACCTGGATTTAATCATGGCTTTGCCATCTGCTAGCCAAGA
GAACTTGAACAAGTGAGTCAACTTCTTGGAGTCTCATTTTCTGCTTCTGTAACATGGGAACTAGGGTAAT
CTAACTCATTGCTTGTGATGATTAGATGAGGCAAAATGCTGAGTTCACCTAGCCCAGCACCTGGTCCATG
GGAAGCATGTGGGTTCTGCTGCTACCCAGTCCTTGGCCCAGTGCATGGTGCACAGAAGGGAATCTGAACA
GGCCAACTTTATTCCTATTCTTGACCCACCCCATGTAGATGCTTCCTACATCTTCAGCTTCTTCTTCTTC
TTCTTTTTTTTTTTAAGGCAGGGTCTCACTCTGTCCCCCAGGCTGAAGTGCAGTGGCACAACCACAGCTC
AGGGCAACCTCGACCTCCTAGGATCAAGTGATCCTCCCACCTCAGCCTCCTGAGTAACTGGGATGACAGG
ACCACACTACCACACTTGGCTAATTTAAAAACTTTTGTAGAGCTGGGGTCTTGCTATGTTGCCCAGGCTG
GTCTCAAACTCCTGGATTCAAGTGATGCCCTCACCTCAGCCTCCCAAAGTGCCTGGAAAACAGGCCTCCA
CACCCAGCCTTCAACTTCATTTTAAAAAATTGTGGTAAACTATACAATTCATCCATGAAAGCAGAAACCA
CTTGTACCCCAAAAGCTATTGAAATTTAAAAATATATATATTAAAAATAAAAATAAAATTGTGATAAGAT
ATACATAATATGAAATTTACTACTTTAATCATTTTTAAGTGTACGGTTCAGTGGCATTGAGTACATTCAC
ATTTTTGTGCAACCGGAACTTTTCATCCTCCCAAAGTGAAGCTCTGTACTTATTTTTTATTTTATTTTAT
TTTTTGAGATGGAGTTTCACTCTAGTCGCCCAGGCTGGAGTGCAGTGGTGCAATCTCGGCTCACTGCAAC
CTCTGCTTCCTGGGTTCAAGAGATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGATTACAGGTGCCCACC
ACCACACCCAGCTAAGTTTTTGTATTTTTAGTAGAGACGGGGTTTTGCTATGTTGGGCAGGCTGGTCTCT
AACTCCTGATCTCAGGTGATCTGCCCGCCTCAGCCTCCCAAAATGCTGGGATTACAGGCATGAGCCACTG
TGCCCGGCCAGCTCTGTGCTCATTAAACAATGACTCCAAGTTCCCCTTCCCCACATCTCCTGCTGACCTC
TCTTCTACTTTCTGTCTCTGTGAGTTTAACTATTCTAGGTACGTCATGTAAGTGCATCTATGTGATATTT
GTCCTTTTGTGTCTGGCTTATTTCACTTAGCATAATGTCTTCATGATTCATTCATGTTGTAGCATGTGTC
AGAGTTTCCTTCCTTTTTAAGGCTGAATAATACTCCACTGTATGGATAGACCACACTTTATTTATCCATT
TGTCTGTTGATGGACATTTGGATGATTTCCATCTTGTGGGTATACTGAGTAATTTTGCTATGAACATGGG
TATAAAAATATCTATTTGAGTTTCTGCTTTCAATTATTTTGGGTCTACACCTCAAAGCGGAATTGTTGGA
AGTGGAATTGCTTTCCACTTGTTGGAAGTGGAACATGGTCTCCCACTTCATTTTGACACAACTTCCAAGC
TTCAGAACTGTATTTACAACAGCGTGCTGGGAGGTCGCTTTGAGTTTATGACGGAAATCTCATATCAACA
GGTTTTAAATTGTTCCATACGACTTCTTGCCACCCCTGTCCCAATTCAGATCTTTTTTTTGATTAATGGT
ATGAACAATTTTCAAAATATCCTGGCACAATCTATTAGAATATTTGACTTTCTCCTCCTCCTCCCTTTAG
CCCTAACTATTTGGCAAAGCTGTTGAAAACTTCTTCACATCTTCTCTCTGCCTCATCTACTTTGCTACTC
AAAGATGATTAGTAGATGTTTTGGTATGATTTTTTTTCCTTGGCATAACTGTGAATACTTTTAATCCTTC
ATGTTTTATGACAATCATACATTCCCACTTTTGTGTAAAAACATTTTGAATTCTTCTTTCTATAACAAAT
TCTTTGCCAGTCTTCCTTTTCTTTTTGCTTTTAGTGAGTTCCAATGATATCATTGTTTGAACCTGTTTTC
TAATTCTATGCTGCTATTCCCATACTCCCTCTTTGCTTTGGTTACAGTAGATAATGTGGGTGGTCCTACC
AAGACAAAGCATCACTCAGGAGTCAAGGGCTGGGGTAGATACAGACACTAGGTACTGCAGAAAGTCAATA
TCTTTCTCAGAGTGTAAGGCAGGACAAGACTTCTGTTCCCTTGTACCGTTGTGGCTGGGGAGTTGGACTG
TGCATTTCATCCTTGTCATATAAGTCAAAGTATTGCCCAAATAACTTAATTTTGGTGTGGTCTTAGTAAG
TATTTGTCTCGTAGATATGTTAAATAGAAGACAGTAACATTGGGTTGGCTGTGTTAATTCCTCACTTTTT
CTTTCCTATACATGAGCTTCCTAAGAAGCGGAACACTTGGTGGTCAGACAGTTGCAGAGATTCCTTGCAT
GATTGCAATCTGGAAAGTAGATACCATTCTTGAATGAAGAGCTTGCCCTTTGGAGAAGCTGGGCTTTCCA
TATATGGAGGTTGTTAGAATGCATAAGAGTTCAGCTTCTGGAATGAAAGGAGACCTTGGTTCAAAACCCA
TCTGCCACTTGCTTGCTGTGTGGCTTAAATCAGGCTTTTAAACTTCAATTATAATTTTGCATCTGTATAA
TAGGATTAATATAATTCCTTCCTCATAAAGTTCCTAGGGGGTTAAATGAAACAATCAATGTATAACACAC
TTCCTGGCATGTGATGTTCAGTACCTAGAAGACTCGGTTTCCTTGGTAGAGAGAATATTTGGCTAGACAA
GCTTATGGAATTACCCCCAGATAGGAAGTGAGCACAAGTGTGAAATGAACAAGCCAGAGCAGGAACGGCT
CTTGGAAGCGTCTACTCAGGCCTGGGCAGTTGCTGGTTTATATAACAGTGCTTTGAAAATTCACGTGCAG
ATTCTTACTATTTTCCCAAATGTTACAGCTCAAAACTATGTTGTCTGTACCTTAACACCTAAAGGATAAT
ATAGTCTTTCACTGATAAAACTAAAATGTCATAGGTTTTCCTTTGGCCAAATATGTATAGAAACTTGTGA
TTTCACATCAGATTTAAAGCTGTATTTAACACTCTATGAAAACATACTGATGCTTAGAAGTAGAAAGGAA
GTCAGATTTTGACATCTTACTTGTCAACTTAAATTATTTATAGTTCCTGGATGCTTCAAAATGTGATAAA
CCATAGTTAATTTTATGTAAATATTCGATGAGTGCCTTTAATAAGGAGACTGTAAAGGTAGCCAAGCTTT
ATATATGTTAGCTACATTTATGGGTCAATCGGGTATAAAAAATAGGACTTCGAAAATAAAATATTATTTT
GTCGGACTCCTCCAATGAGGCTTTTTCGCAGGATTAGCTAAAATTGGCTCTTATTTGATGTGTGAGTGCT
TAAACATTGGAGAATTCATTTTTCTTTTAGAATTCATTTTTATTTCTGAGCCTTAAAATATGAACAGTTA
GCTAAATGTTTGTATATGTTGATAAGGAATGCTAAGTGTTTATTCCTTAATGGGACGACACCTTTTCCCG
GTTTACATAACTTGCCTTTTAATCTAACCTTATGAAAGTCTCCTTGACTTTAATTTTTTTTCAGAGTACT
GTATATCTCTTTAGGGAATGCATTTATTTAAAAAATTATAAAGCAAGAATAGATGTGATATATTTTGAAG
TTTTCTAGTCACAAATTAAATCCCTAGATGTGTTGTAGTTTGTGGAGCACTTTGAAATGTGCCAATTCAA

GATGGAAATAGCAGGAAAGAACCATTCAAGTACGATTTCTGACTCCATAAAGTTAGGAAGTTATGATAAA
GGAAAAAATAACTACACCACATACTTATGGCACAGAATTGCATTATTGGGACAAATTGATCTTCAAATTTG
TAGGCTATGATGGAAGCAAATATTTGTAGTATCTTAATATTCAACTGTTAAGCCAGGAGACGAGTACTCT
GAACTTCAGCTTCTCATAAAATCAGTCAGTTACATGACAGTTTATGTAGTTTATATGTAAGAAACCCTTT
GATCAAGATATGCCTTTTCTTCAGCCTTGTTAATACTTCATTTATAAGGATTTTTATTTCTAGGAAAATA
ATACCATAGACCTATTTTATTTAAAGCTAAAGTGTTTCCTGGTGATGGTGGTGAATGGGGAGATGATTCA
AGGAAACTGCTAATCTTGTAGAGTTTAGTAAAATCTTGGAATAGAAATTTTAAAAAGTTAAAACACACTA
TGAAAACAAATCATTATTAGTAAAATGAACCATATTAAAATGTCTCCATAACCAACGTATTATAGCAGGG
GAAAATGGCATTTTAATTCAGAAAAACATTTCTATATAAAACAAGCTTTGGAATAATTTGAATATGTTGA
TTTTTCTTTGGGGCAATCATGAAATACAGTCATATTAGGAAAGAGGCAAGGCCTCAAAACGGAAAGAGTA
GTGAGGATAATTCATGAGCAATGCGTGGCTTCATGGATCCCTTCCTGGCCCTCTTCATCTATGAACATCT
GCTTTATGTTCATGTCTGGCCTCACCCAGTGCTGAAGAGCAGACTGCCCCTGCTTAGAACCAAGCCTTGT
TCTTGTGGATTTGAGTTTTGGGGTCCTGAGGTAGAATGGCCATCATATTGTTCAGGGTCCTCACCTTCCC
ACTCATTACTTCCTTTATAGAACCCCAGTCATCCCCCTCAGGAGGCCTGCGCTCCACAAATGAAGTTGGG
GGTGAGGGGAGCTTTAGCATCTCAGTATTGTTCAGATATTGGATACTTGTTGAGCTCCACTATGTGTGTG
AGAATGCGCTGGGCTCAGGATCAATAGCCATAAATGAGACAGATATGGCCCATCCCTTGCCATGCCTAAA
CTGATCTGGGCATTGAGACAAGCAGTTAAAACCCAACATAGTAAGTCCTATGATGAGACACAAACTAAGC
ATGGCTGGAAGGGCAGATAAGATTTCACAGAGGAACTGACATCTTGACTGGCACACTTAGAAGATGAGTA
GGAGTCAGTTGGGCCAAGAGGAGAAAAAGTGTGTTTCCATGAAGAAGAAGAGCATGTGCCAAGTCCTGGG
GGTGAGAAGCATGGCATGTGTCAACAGAAAGACATGATCAGAGCTTGGATGGGAGTTAGAGCGGGGAGAG
AAGGCAAGGAAAAACATAAGAGCTTTGCAAACTGTGAAGGCATTGCATTTAGATGTCATTTTTAGAGCTT
GGAGGAGCCTCAGGACATTGAGGCAGGATAGTGGCCTGATGGCGTATGATTTTAGGAAAAATCACTGTGG
CCACCCTGTGGGGAAGGATTGGCGGGGGAAGGCTGGAGGCAAAGGGTCCTGCGGTGGGCTGTGGTAATGA
TCTGGGCTGGAGAAGGTATGGTGGTGCCCAGCGCAAAATTGGTTTCGCTTTGAAAAATAATTAGAAAATA
TTTGTTTTGATCTGTGTGCCTGTGGTGGGAGGTGGGGAGGGAGGGTCAAGTGAGGAAGGAGATTGAATCT
AGAATAATGCCCATGTTTCAGGCTTCACGTGCAGACATTTCTTGGTTCAGCTGGGAAGTGAATAGGAACA
GACTGGCGAGGAAAGAAGACAGTCGTCAGTTCTGTCTGGGGCACATCCATCTTGACGAGTGTGAGAGAGT
CAAGTCTTGATGGACAGGGGCAGGTGGACATTCAGGAAACTCAGGAAAGAGATTTGATCTGAAGTGACCA
CCAGAAAATACTGACGGAAAAGAGGTGACAAAAGGAGAGACCTGCAATATTATATTGGCTTTCTCTCAGG
CAACTGCTTGGCCTGTCTTTATATTCCTTTTGAATCTCTGCATATGTACGGGCCATTATTTATTTTCACA
ACTAACAAATGCAGACTTTCTGTGTAATGACAACAAAGCCAAACCAGCTGCTACCAAAGGAGGGAAAATC
AGAAGAGAAGGAAAAAGAACAAGGGAAGCTTGGGGAAAAGCTGAATGTGGGTCCTTCTGTTGCTGCAGGG
GCTGGGGTGGGCCCGGTGATTCCTACTGAGAGGCGTTTTCTCTCCCCGCTTCCTGTCTTTCTGGTTCCAT
CTCATTCACCTCCTGTCCCCTCCACTTCCTGCCAGTCAAACCTTAGATTCCTCCAGAGGCTTTTTATTTT
TATCTTTTGATGGGCAAGAAAATAGTGCGGATTATTTTTCCAAACCTTCACCTGAACATCACATCGTGGC
TTTGGCCCTATGGGCTTGGTTCATCCGGGCCTGCACAGAAGGACTTTTCGGGCCAGTCTGGTCACATACA
TCGAGTCCTGTCTTTTCAGTTAAAAAAAAACACACACACACACACTGCTATGTTTCACTAAGACAACTGG
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GATAATAAAATTTAAAAAGAATTTCTTCTTTTTTTTTTATTATACTTTAAGTTTTAGGGTACATGTGCAC
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GCATTAGGTATATCTCCCGATGCTATCTTAATGCAACTTAAATCAATTGCTTTAATAACACATATTGACC
AAGTTACACTCATTAAGGAAAAAAAACTACTTTGTTGTTTTTCTTCTTCTGACGTGAGCTGAAGACTTAG
AAATAGTTGTTAATAGTGTTTGGTTAATAAGAATTTGTTTTAATTGCATATATCAAATATGTATTTATTA
AACTTTTCTTTTTGTCAGTTTATCAATTCTAGCTTTGTCACAAAAGGTTTGCCGTATGAACATGATTCTG
TTGTACATCTATTTCCATTTTTGTTAAGAGACGAATTCAATTGTAAAAATCTAGTACCTTTTATTCATTA
AACATGTTAGTTCAGGAATTTCACTTGGTTCTACAAAGATACATATCTACAGTGGATGGCCAGTGCAAAC
ATGAGACTCAGCCAACTGGTCTCTGACCCAATTCAGTTCTCCTGTCTTCTTCTGGCTTACAAAGTAACTG
GCTCTGGGGAGAAAGTGAGTCAAAGTAATATTTGGTTTGAATGGTTATTGACTATTTTCTTCTGAAACTT
AATGTATACTAATTAATTTTTTTATTTTATTCTTTTTTTTTTTAGAGATAGGGTCTCGCTCTGTTGTCCATG
CTGGAGTGCAGTGGTGCTATCACAGCTCACTGCAGCCTTGACCTCCTGGGCTCAAGCGATTCTCCTGTCT
CAGCCTCCCGAGTAGCTAGGATTACAGGCATGTGCCATCATGCCAGGCTAATATTTAATTTTTTTTTTTT
GTAGAGACAAGATATTGTTATGTTGCCCAGGCTGGTCTAAAACTCCTGGTCTCAAACTATCCTCCCACCT
CAGCTTCCTGAAGTACTGGAATTATAGGCATGAGCTGCCACACCTGGCCATATACTCATTTTTTGTTAAA
AGCTGAAATATATCAGCATATACTGCATAAATACCACAGGAGACTAAACACTGAAAGTTTCTTTAGGGTA
TCAGAAGAATACACTTTTTGCTTGCAGTTAGCATCTGCACAGATAAGTTTTGTTTCTGGTTCTATTACTT
CTTCAGTTTGACCCTATTAATAAGGACAATTCTAAAAATAATAACTGTGTCTGGATATCTGAATCCGTGT
GTGGTCTTTTACTGAAGTTACAGGTTTATAACTCTGCTGACTAGTTTGCTGGTTTCTGTTATGCAATAGA
AGAGTGCAAATGTTAATTTGATCTGAAGCCCGTGTATACAGTGACTTTTATAATGTATATTTAAAGATGG
AAAGCCAAGTTTTATGAGGCCAGCATTTCTTGTCAAGTCCTCACTCCACCCTCTTCTAATTGGGCCTGAC
CCTTAAGTTGAATAAAGAACAAAGAGCTCTGTAGTTAAAACATTTCACTGCATGTTGCATCTTGCCCTTA
GTAAATGGAAAAAAATAGAGACTTAAGCAGAGAATCTGAACTAGGGTGTGAAATATATATTCAGTTTTGG
GGTGGGAGAATGAGAACCATGTTTTACAATAGTATACATAACTTCCTTAGTCTAAATTCAGGACATTTCC
CCAAGATATGTAAGAATTTAGACTTATGCAGACAGACTTTATAAAAACATGCCAATATTTATTAGTTTGT
GAATTTTAATATTCTGCTCCCTATAAACCAGATTTATTTTGAGGGATAAAGGGATGGAGGTGACTTCTAA
ATCTTAGAGCAGAAACTTCCTGTGGGCAGCTGGACATATGTACCAGGAGCTCAGAGAAGAGGGTTGTGTT
GGGAGCGTACATTCTGAGTGATCTGCATTTGGTGATGATGGAAGCCATGGACATGCACTAGATTGTCTTG
TGGGAGAATATGGAGTAGTAAGAGAAGAAGAAGACCTAGGATTGAGCCCTGAGCACCTCTGGCTTAATGT
TGGATGGAGGAAATTGAATCTGTAAACAATACCGGGAGGCTGCAGCCTGAGAGGCAGAAGGAACTGGGGT
GTTTGGGATTATGGAAGCCAAGGGAAAAAGCCTGTCTCACAGCGGGAAGGGAGGTATCAACATTGTAAGC
TGCTTCAGATAGGTTATGTAGGATGTGGACTGAAAAATACCTGTAAAATTTGGCAACGCGATTCATTGGT
AATCCTAGGGAAGTTGCTTTTTTGGGGTAACTAAGGTGGAAAACAGATTGGTGTGGGTTGAGCAATGCAA
GAGAGGTGAAGAAAAGGAGATTTCATGTGCAGACGTTTCTGAGTTCAGCTGGGAACAAGGGATAAGATAG

AAGATGGAAGTTAGAGAGCATGTGGGGCAAGGGAGACTCTTTTATGGGACAGTCTCGCATGTGATCAAAG
CCAATGAGTAAGGAGCATTTGAGGGAGAGAGAGTCAATCAACAAGAGAGAAAAGAAAGAGGGTTCATCAT
AAAATAACGGTAACAACAACGAACATCTTTTGAGTGTTTTCTATATCCGGGGAACTATGGTAAACTCCTA
ACCTGCATTCTCACATTCAATTCTTAGAATCGTTGGATGTGGTGGGTTCCATGATTTCCTCTAGATTAGC
GAGGAGGAAAGAGAGATCTAGAAATGTCAGGTAGCTTGCTCAGAGTTCTCCAGGTAGTCAGTCATGGACT
AATTTGTGAACTGAAGGACTGAACTTCGTCACCACCCAGCCCACCAAGCCGGCTTGACTTTAGGTATTCT
GTGCTGCATGTGAGTACCGACTTAAATTATATTTTAAGAAGGGCTACTTTGAAACTCTCTCTCTGAAAAC
TCTATTTCTAAAAGCTCTACCCTCACAACAATTTTGGCAAGCAGTCTTGGTAAAACCAAACCAAACCAAA
CCAAAACCAAAAAACCTTATCTGCTGAGAAAATATAACCACATAAAATATGGTGCTACAAAATATAGACT
GTGTGAACTGAAGGTGACTTGCCCAAAGGACTCCTGAAGCAATTGGCTGCTGTAGAAATTAAGTCCACGG
GAGGTTTTTGTTCTGTTTTTTTTTTTTTTTTTTTGAGATGGATTCTCACTCTGTTGCCTAGGCTGGAGT
GCAGTGGCGCAATCTCGGCTCACTGCAACCTCCGCCTCCCGGGTTCAAGCGATTCTCCTGCCTCAGCTTC
CTGAGTAGCTGGGATTACAGGTGTACACCACCATACCCAGGTTTTTTTGTATTTTTAGTAGAGACGGGG
TTTCACCATGTTGGTCAGGCTGGTCTTGAACTCCTGACGTCGTGATCCACCTGCCTCGGCCTCCCAAAGT
TCTGGGATTACAGGCATGAGCCACCGTGCCCGGCCCATGAGAGGTTTTGTTTGCACTTCAAGAAGGACAG
AAAAAGGCAGGCAGGCTGGGGAGCAACATAGTAAGGCTGAGGAAGTGATAGGAAAACAGCCTCCAAAAGG
TTTCCCTGTAGATTCTGACTGGCTAAGTTTCCTGAAATAATATTAATTCTGTCCTCTTGCTTTTAATAGG
ACATAACGACTATATGTGTCCAGCCACCAACCAGTGCACCATTGATAAAAACAGGAGGAAGAGCTGCCAG
GCCTGCCGGCTCCGTAAATGCTACGAAGTGGGAATGATGAAAGGTGGTAGGTACATCTCTCCCAGGGGCC
CTTGGGGATGGCCCTGGCCACCGCCCAGTGCTGGCTCTACCCATTGGAATAACACCATGGGAATTTTGTG
TTTTTTTCTTTTAATTGTTTTTTTTCTATTCTTATTTTTCTTTGCAACAAAAGTATTTTCATAATCCATT
TTATTTTAAAAAGGTGGAAGTGTCTGGAACTGGAAATTCTAACATGGCATTTTGTGTTTTGGATTTTCAA
TGTAAATAATTATATTTTAAATCAAAGGTGTGTGGGAGGCGGTGATGGAAGGAAACGAAGAGTGCTTAGT
AAATTATTCTAGAAATATTTTTCAGTTACTGTTTATGTTGCAAATGCTAGAAAATGATATCTGAGGATAA
ACTTTCCCTAAATTGAGACTTGTAAATGTGAAAGCTGAGTAGCTAATTTATAGCCTTCCAGTCTGTTATC
ATCCCTTAAGGAATGTGAATTTCAATCAAAAGGCAGTTTTCTCCTTTAGAACCTGAGTGAACCAGCCACT
TTCTTAACCTCAGTGTCTAGCATGGTGCTGGCATAGTTGATTACTGAGCACTACACTAACAAGTGTCAGA
GCATGCATGGTTTGTGACTGTGGGTTTGTGTTTTTGTGGTCTTTGTGGCTGTGTGTGTGTGTGGTTTTCT
GTCTTCTCATGTATCCGATCTTCCAGTTTTGTCATACAGGAATCTGGAAACTGAATCCCAGTTCTGGGAA
TATTAGGAGCCCCATAAATGTGGTTGCCTGATTGACCTCATTGTATTCTTGGGAGTCTCATCTTGAGGAA
CATTGCTTCTAGTCTTGGATAGCCTTCAGTGTAGTGGAAGAGAACAAGTAGAAAATGTGTAATTAAAATA
AAGTCATGAGGCTGAGGTGGGCAGATCATCTGAGGTCAGGAGTTCGAGACCAGCTTGGCCAACAAGGTGA
AACCCTGTCTCTATTGAAAATACAAAAATTAGCTGGGTATGGTGGCGAGTGCCAGTAGGCCCAGCTACTT
GGGAGGTGGAGGCAGGAGAATCACTTGAACCTGGCAGGTGGAGGGGGCAGTGAACTGAGATGGCGCCACT
GCACTCCAGCCTGGGTGATAGAGTGAGACTCTGTCTCAATAAATAAATAAATAAATAAATAAATAAATAA
ATAAATAAATAAATAAAGTAACGGATTCATTTAGTGTTTCAGAAGGATACTGAAGGGAGGGAAGGGCTGA
TGATGGTGCTACCTGCTGATTGTAATAGGGAAAAGCCCGTTTCTTTTCTGAAGGAGGTGAAGCTTGGGGT
GATTTAAGGAGAACAAAATTTCAATGAAAAGGAATAGTGATTTTGCAAATAGTGGGCAGCTAACCTTTAA
ATCATTCTTACTGGGACGCAGGAGGAAGGAGAGGAAAGACCAAGAATGGAGATTATGATGAAGACAAGCT
TGATTGTTAACAAGCTTACAGTGACAGGTTTCATAGTCCCGGGGTCATAAATACGCCAGACAGGTTGAGG
TTTGGAATGCAGCATTTGGAATAAATTCTCCTGGTGAAGAGATGCAATGTTGAATTTACGCATTCTGTGA
GCTGTGACTATGACTATACATCTTGAACATCTGAAAAAGCAGCTTTAATTCAAAGGGTAATTAATTCCAA
GAATTTAACAGCTACATTCAGAAAATGACACTTGAGTCATATGGATTAAATATTTAAGGAATTCATCTTT
CTTTGTACTGTTGGAGAATTAGTCAGGCTTAATTAAACTTACAAAATGCGTCTTAAGGTAACTTGGTAAG
TGACAGGAATATAACAGCTGCATAAGAAAAGCTTTATTGAAACAGTGGAGTCGAGGTTTAATATTCTTC
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ATTCTGTTTTTTTTTTTGTAATTAATATCCAGATACGGTCTGGCTGCATGAATATAAATTACGCATTCTC
ATTTTTAATCTAACAAAAATTCATATATGCAAAGACATAATAAAAGTCTCCCCACTGTTTTCTCCTAGGA
ATCTAGATAATTTGACTGTACACAACAGACTGTGGATGGCTCCATACACACTTGCACATGTATATTGATG
ACTGTAAAATATATATCTGTATTAGTTTTCTAGGGCTGCCATAATGAAATACCACAGGCTGGGTGGCTTA
AACAACGGAAATTAATTTTCTCCCAATTCTGGAAGCTGGACATGCATAATCAAAGTGCTGGAATATTTGG
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GTGGCACTATCTCAGCTCACTGAAACCTTCACCTCCCAGGTTCAGGCGATTCTCCTGCTTCAACTTCCCA
AGTAGCTGGGACTACAGGTGTGTGCCACCATACCCAGCTAATTTTTGTGTTTTTTTTTTTTGTAGAGACG
GAGTTTCACTCTATGTTGGCCAGGCTGGTCTTGAACTCTTGACCTCAGGTGATCCGCCCACCTCGGCTTC
CTAAAGTGCTGGGATTATAGGCGTGAGCCACCATGCCCGGCCTGTGAGGCCTCTCTTCTAGGCTTGTGGC
TAGCCGTCTTCTGCCTGTGTCCTCACATGGCCTTTCCTCTGCGTCCGAGCACTCTTGGTATCTCTTTCTC
TTCTCACAAGCCCTGTTGGATTAGGAGTCCACCCTTATGACCTCATTTAACCTTAGTTACCGCCAAAAAG
GCCCTATTTCCAAATATAGTCATACCAGGGGCTAGGGCTTCAACATACAAGTTTTGTGGGGACACAGTTC
ATAACAGGCTGCCCTCCCAAAATACCATAGACTGGGTGGCTTAAGTAACGGAAGTCAATTGCCTCATAGC
TCTGGAGGCTGAAGTCTGAGACTAAGGTGTTGGCAGGTTTGATTTTTCCCGAGGCCTCTCTCCTTGGCTT
GAAGATGGCTGCCTTCTCTCTGTGTCCCCACATGGCCTTTTCTCGGGGCATCCACAGCTTCTTCTTCTTC
TTACGAAGACACCAGTCATATCGGATTAGGGCCCCACACACAGGACCTCATTGAATCTTAATCACCTCAC
TTAAGGTACAATTTCCAAATACAGTCACATTCTGAGGCCCAGGGGGTAAGATTTCAACATATGAGTTTTA
AGGGTACACAATTCAGTATGTGGCAATATCCCATAGGGGTTACTCAGTGATTGTTCAGTATTTCTTTACA
TGTAAGGAAAACATGTATCTTTCTGGCAGTTTTTATATGTACATAAGTTTTAAATGAAGCTTTAAATTCA
TAAAATTATAGCCCGTGAGAACATCTTATTTTAATGATATGTATAAAGTACTTGCCATAAATCAATATAA
TTTATTGTATTTTCTACAACATGGAATACCACACATGGCCACAGGATACCCTCTATAACAACTCCTTGAA
AAATCCCATTGAATAAAGCCTTAATTTACAACTGGAAGTACAATGATAACTAACTATAAAATGTGCAGTC
ACATGGCAAAGGCCAGCTGTGACTGAATAAATCTTTACAACATGTTTTCAACCATTAGGGTTCACAACAA
TCCACTTTCTTAACCAGGCTGGTTACCAACTAGGATATTGAAACTCTACCTATGAAATAAAAAGTTTAGT

FIGURE 1, page 49 of 93

TTCAGTTAAAAGAGAACCACAGACCTACTCCCTATTTTCATAGCAAGGCTGAAAAAATTCACTGAAGATC
TATTGTAAAGATCCAAAAGAGTGCATGATTTGTCTCCATGAACTAACAATTTTAATCTGTTATAATACTT
ACTGCCTCTGAAAATCCCAGCATCATTATTAGATTTGGTTCTGAATCATGGTAGTTCTATAAGATGCAGG
ATTTGAATTGCACTTTCGGGAATGTGCTTTTCTATCCTAGTACATGTGCTGGTTTCTCTGCATTGCTTTT
TCCTCTTCATTTGTCTCCTTCCTCTTGAACTTTAGGTTGTAGATTACATGTCTCTTCTTCAGGAAGGCCT
ACACAGTTACCTGACAGTTCCTGAGGCTCGAAGTTCAAAATCAAGGTGCTGGAAAATTCATGTTCTAGCT
TTAATGGCAAACAGCTCTTCTCTTAGCTCTTATCACCATTATTATTAGTCATTCAATGTCTGTCTTTACA
TATGGTCCATAAACTCCATGATGGCGCGGGGGTGGGGGGTCTCTGTGTCTTGTTTACCGATCTTGCATGA
AACAAGTCACAAGGTAGGTGTTCAAGAAGTATTTTTTTGCACTAATTAATGAATTGATTCAATTCATTTA
AATAGTTATTTGTGTAGGGCTTCTTATATGCAAACCCTTGGGAATAAAGCAAATATGAATAAGATTGTAG
TCCCTTCCCTCAATGTCCTCACAGTATAAAGAGAACATTTGCATGGGAAGCGGCAAATAAAAATCTCAAC
GGCAAGTGGAGACTGGGTTGCAAGATGGCTCAAATATTGAATGATCAGAATGGGAGTCTAGAGCTTTAAA
CAACCACTCCCAGGTTTAGTCCAACTCAGAGTATTACTCAGACACCTGACATCCAAGACATATATTATTA
CTCAAGAATGTGGCCTTTTTGCTGAGTTTGGTAGAAAGAGGAACTCTTCCAAAGATAAATGTGTTCAAAT
GCTGGCTCCTCCTCAAACTTGCTGAACAACCTTGTTAAAGTCACTTTTATGAGCTTCACTAATTTCAAAT
ATGAAATGGAGATAAATAAATTTTATTGTCCAAGCACGGTGGCTTACGCCTGTAATCCCAGCACTTTGGG
AGGCTGAGGTGGGCGGATCACCTGAGGTCAGGAGTTCAAGACCAGCCTGGCCAACAAGGTGAAACCTCGT
CTCTACAAAATTAGCCAGGTGTGATGGCAGAAGCCTGTAATCCCAGCTACTCAGGAGGAGGAGGCAGGAG
AATCACTTGAACCCAGTAGGCACAGGTTGCAGTGAGCCGAGATTGCACCACTGCATTCCAGCCTGGGCAA
CAGAGTGAGACTCTGTCTCAAAAATAAATATATAAATAAACAAATAAATAAATTTTACTTAATGAGTTTG
TCATGAAGATGACAAATCGTAACATGGGAAAATATAAATCTAAAGTGCCACACAAGTGTTAGCTATTACA
TATCTTTTTTGTCTTAAAAATAATTACTATCTTAGTTAAAAATTTCATCATATACGAGCACTGCTGGGTT
TTTTTTTTCAGCTGAAAGAAAGAGAATGGCAATTTCATCACTTCTACAAGATATAAATTTCTAATTTCTT
TGTGGAGAATAAAAACTTGGCTTAAACACCTAAGCTTTTTTTTCTTTTCTGATCTCATATGCTGAATATA
GCTGAATGACAAGTGAGATGTGTTATTTATCATTTTATGATGCCAGAGATTTACACGAATTTGTGAAAGG
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ATAGAAATCAATTGATGTGCAGGACTCTTGGACTGACTATTCTGGTTATGTTTCCTTATAACACATTAAG
AAGAAATTTGAGATAAAGTAGTAATTGTCAACTAGTCTTTATTTATTTTAATAACAAATGTTGCAGTATA
ATTTTTAGAAATATTCCAAAATAACAAATAAATCCAAAAATTAACGGGATAATTTTAAAGTGAGAAAATA
ACATACTACTAATATAGACAGGGAAATATACATGTGTCCAGAATGATTCAGAAGCCCAATGAAACACTGG
AAAATAAAATATTTTCCTGTTGCTTGGGTTTAATATTTATCACTATGAGTTATCGTAATTTGCTTTATTG
ATGGATAAACTCCCAACCTGGGGACTGCGATTGGAATCCTCTTTAATCCTACATTGGCTATCCTTTATCA
AAAGTAAACAACCGGCTGGCCATGGTGGCTCACACCTGTAATCCCAGCATTTTGGGAGGCCGAGGCGGGT
GGATCACCTGAGATCAGGAGTTTGAGACCAGCCTGACCAACATGGTATAACCTCGTCTCTACTAAGGATA
CAAAAATTAGCTGGGTGTAGTTGTGCCCACCTGTAATCCCAGCTATTTGGGAGCCTGAGGCAGGAGAATT
GCTTGAACTCAGGAGACGGAGGTTGCAGTAGGCCAAAATCACACCACTGCACTCCAGCCTGGGTGACGGA
ATGAGACTCCATCTCAAAAAAAAAAAAAAAAAGTATACAACCAATTATTAATGTTCATGATGGTAGAATCA
AATTAATAAATTAAAAATGTAGATGTGAATTACTTTTTTTGGATTGCCGAATAATTGTGGAAGATTTGTA
GCTGCATGTGAATCCAAGTTTCCTCAAAAGGTAGGTTGGGGTGCTCCTATTTAGGATTGAATTTAAGAAA
AATGTTAAAGAAAAGCTAGCTGCTCTTTACCAAAGAGAGACTGGTTGTTTTAAGCAGTAATCTAATCTAT
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GAATCCAATGTTTGACAGTATTTTATATCAATCAAGCTCTGGTTTCCACAAGCAGAAGCAGATCGTCATC
TATGAAACAGATAAAAGTTGATTTGGCATACCCTCTCTTTATTCATTATGATGTTCATGAGAAACCTTCT
TAGAACCCTAGGGCTCCAAGGAACACAGTTTGCAAGCCACTGATCTAATCTAACTCCTTCATCCTCTAGG
TATGAAAATCAAGGCCCTCCATTACCTATTAGGGATGAAGGCAGGTCAGCCTCTGTGACTGTCAGTTCAG
CTGGAGGAAGCATGAGTGTAGGCAGCACAACAATCCCTATAAGGACCATGTTCTTAAGCTGGTTTTTTTT
TTCCTAGTAGTTTTTACAGTTTCAGGTCTAACATTTAAGTCTTTAATCCAGGTTGAGTTGATTTTTGTAT
ACGGCATGAGATAAGTGTCCAATTTCATTGTTCGGTGTGTAGATATCCAGTTTCTCTAGAAACATTTATC
AAAGAAACTGTCCTTTCTCCATTGTGTGCTTTTAGCAGCTTTGTCAAAAATTAATTGGCTCTAAATGAAT
GAATTTATTTCTGGGTTCTCTATTCTGTTCCATTGGTCAATACATGCTGTTTTAATTACTATAGCTTTAT
AGTATATTTTGAGTCAGGTAGTGTTATGCCTCTAGCTTTGTTCTTCTAGCTCCAGATTGTTTTGGCTATT
CAGGGTTTTTTTGTGGTTCCATACAAATTTTTGGATTGTTTTTCCACTTTTGTAAAAAATGTCATTGCAA
TTTTGATAGGCATTGCATTGAATCTGTAGATTGATTTGTGTCATATGGATATTTTTAACAATATTAATTC
TTCCAGTCTATGTATGGTATATCTTTCCATTTATTTGTGTCTTCTTCAGTTTCTTTTATTGATGTCTATA
GCTTTTAGCATACAATTCTTTCACTTCCTTGGTTAAATTTATTCCCAAATATTTTGTTTTATTTTTATAG
CTATTATAAATGAAATTTCTTCTTGATTTCTTTTTTTGGATAGTTTGCTGTTAGTGTATAGAAACACTAC
TGATTTCTGTATGTTGATTTTCTCTTCTGAAACTTTACTGAATTTGTTTATTAGTTCTAATAGTTTTTTG
TGTGGAGTCTATACTTACATGATCTATGTGTAAGATCATGTCATCAGCAAACACGGGCAATTTAACTTCT
TCTTTTTCAATTTGCATGCCTTTATTTTTTTTCTTGCATAATTGCTCTGGCAGGAACTCTCAGTACTATG
TTGAATAGAAGTGGTGAGAGTGGGCATCCTTGTCTTGTTATTGATCTTAGGGGAAGACTTTTCAAATTTT
CACCATTGAGTATGATGTTAGCTGTAGGCTTGTCATATATGGCCTTTATTGTGTTGAGGTACACTCTTTC
TATATTTAATTTGTTGAGAGTTTTTGATATGAAAGGATTTTGAATTTTGTCAAATGCATTTTTTCCTCTA
TTGAGATGATTGTATGGTTTTTGTCCTTCATTCTGTTAATGTGTGTACCATAGTTATAGATTTGCATATG
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AATCAATTTTGCTAGTATTTTGTTGTGGATTTTTGCATCTATATTCATCAGGGATATTGGCATGACATTT
AATTTTCTTGTAATACCCTTGTCTGGCTTTAGTATCACAGTAATGCTGGCCTTGTAAAATGAGTTTGGAA
GTATTCCCTCCTCTTCAATTTTTGGGAAGAGTTTGAGGATTGGTATTAGTTCTTTAAATATTTGGTAGAG
TTCAGCAATAAAGCCCATTAGGTCCTGGGCTTTTCTTCCATAGAGGACTTTTTATTGCTGATTCAGTCTT
CTTTCTAGCTATTGGTCTGGTCAGACTTTCTATTTCTTCATGATTCAGACTTGCTAGGTTTATGTGTCTA
AGACTTTATCCATTTATTCCAAGTTATCCAAGTTGTTGGTGTGTAATTCATCATAGTACTCTTATAATTT
TTTGCATTTCTGTGCTATCAGTTGTAATGTCTCCTCTTTTATTTCTGATTCAGTTTATTTGTGTCTTCTC

FIGURE 1, page 50 of 93

ACTTTTTTTCTTAGTCTAGTTAAAGGTTAATCAATTTTGTTTATCTTTTTAAAAACAAATTCGTAGTTTC
ACTGATCTTTTGTTTTGTGTTTTTAGTCTCAATTTTATTTATTTTTCCTCCGATCTTTATTATTTTCTTC
CTTCTACTAACTTGGGGCTTAGTTTATTTTTATTTTTCTAGTTATTTGTGGTATAACATTAGATTGTTTG
AGATCTTCTTCTTTGATGAAGACATTTATTGCTATAAACTTCCCTCTTGAAAATACTCTTGCTGCATCCC
ACAAATTTTGGTATGTTGTGTGTCCATTTTCATTTGTTTCAAGATATTTTTCAACTTTTCTTTTTATTTC
TTCTTTGACCCACTGGTTGGTTCTGAGTATGTTGTTTTATTTTCAAGTATTTGTGAATTTTCCAAAATTA
TTCTTGTTGATTTATAGTTTCATATTATTTATGGTTGGAAAAAAATACTTGATATGGTGTCAATGTTCTTA
AATTTATTAAGACTTATTTTGTGTCCTAACATATGAACTATACTGTTTTTTTCTTTTTTTTTTTTTTGAG
ACAGAGTCTCACTGTGTTGCCCAGGCTGGAGTGCACTGGCTCAATCTTGGTTGACTGCAACCTCCGCCTC
CTGGGTTCAAGCTATTCTCATACCTCAGCCTCCCGAGCAGCTGGGAATACAGGAGCACACCGCCATGCCT
GGCTAACTTTTTGTATTTTTTAGTAGAGATGGGGTTTCACCATTTGGGTCAGGCTGCTCTCAAACTCCTG
ACTTCAAATGATCTGCCCACCTTAGCCTCCCAAAGTGCTGGGATTACAGGAGTGAGCCACCGTGCCAGGC
CATGATCTATACTGTTTTATCTAACATTCAGTGGATAATGTTCCATGTGTATTTGAGAAGAATGTGTGTT
CTGTTGCTGTTGGATGAAATATTCTGTATGTATCTGTTAAGTCCATCTGTGCTAAAGTATAGTTTAAGTT
TGAACTTTCATTATTGATTTTCTGTCCGAATAATCTGTCCATTGCTAAAAGTGGGGTACTGAGTTCCCCA
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AATGTTGGGTGCATATGTATGTTCACCTGTTATATCCTCTTAATGAATTGACCCTCTTGTCATTATTTAA
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CTGCTTTCTTTTGGCTTCTATTTTCATAGAATGCCTTTTTTGGTCCCTTCGCCTTCATTCTCTGTGTTTT
CTTAACCATGCATTGAATCTCTTCTAGACATCATATAACAGGGTCTTGTTTTTTTAAATCCATTTACTCA
CTGTATCTCTTTCTTCCTATCTTGCTGTCTTCCTTTGTGATTAGGCGATTTTCTATAGTGGTATCCTTTG
AATTCTTACTTTTTGCCTTTTGTATATTTGCTACAGGATTTTGCTTTGTGATTACCATAAGGCTTACATA
AAAGATCTTATAGTTATACCAGGCTATGTTCAACTGTTTATAACATAACTTTGATTAATTTTTTAATACT
CAATTTATTTGATTGCTTATTTAGAGATAATTTTGATTCCTATCAGAAGAAAACTGAGGTATCTTTATGT
ACCTTTTCAGGAATGACCACGTCTCACCTTACCTTGAATGTTACAAGAAATGCTGGCAGTGACTCAAGGC
CAGGCAAAAAATTTCAGAAAGGGTTTATCTTGTTTGTACAATTTTCTTTTGCAAAAATAAATGATTCTTGA
TATGATGTAAGGACTTTTTCCGTAGATAGAACCTATAAAATGCAGAACTTTGGGGCAGTAATTATATGAA
TGAATTGCTACTTTAAAATTCTGTAAGTCCCCAGGAATTTCCATATGCTTTTTTTTGTTTGTTTCAGTGG
TTGTGATCAGGCTAATGGGTAGTTTTAGAGCTGAAAAGAACTTAAAGATCATCTAGTGCACCTTTTTGT
TTTTCAGTTGGATTGTTCTTGTCCAAATCACTAAGCTAAGTTAACTGCTCAGACAGGAAACCAAGTCTCC
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AGAAGTACCAAAATAAATTTATATAGACGGTGTCACAGATACTTTAAAAAGACCTACTTAAGATTTAATT
ACCTAATATTATTTAATATTTAATATAATTTAAAAGGGGCATTTTTATCTTTCAGCCAAGGTTTTAATTG
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AAGCTCAATTTAGAACAACTGCGGGCAACTGTAAAAACCGGTAGGAATGGGCAGAGTTATTGTCTTCACT
AGTCATTGTGGAAAGTGAATCTCTTCTGAATGGAGAGTCACAAAAATGAGTTTGATGCTTTCATGATAGT
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AGAGGCCAAAAAAGATAATGAATTTTGGAAAGTTCCTGATTAAATATCGCATAGGCTAGTCTGGTTATGT
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ATCAGAAGTTCCAGAGCAGCCTGGCTAACATGGTGAAACCCCGTCTCTACTAAAAATATAAAAAAATTAG
CCGGGCATGGTGGCGGGCGCCTGTAGTCGCAGCTACTCGGGATACTGAGGCAGGAGAATGGCGTGAACCT
GGGAGGCGGAGCTTGCAGTGAGCCAAGATCGTGCCACTGCACTCCAGACTGGGCGACAGAGCAAGACTCT
GTCTCAAAAAAAAAATTAGCCAGGCATGGCGGGGAGCGCCTGTAATCCCAGCTACTCAGGAGGCTGAGGCA
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TTTTTATATTTTATATATAAAATTTATATTTTTATATTTAGGTGATTATATTTTTAAACGCTTGCTT
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TATTTCAATACAGAATCAACATTTAAAAATTATTGATACATTATGTATGTTTTTTTCCTTCACTAAGACT
TCCAAATCCTCCAAGTGTTTCACACTTACATCTTATTTTGGACCAGCCAGATTTTAGTGCTCATTTGACC
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TGTCAAACCAGGAGTTTGAGATCCCTGAGGGATATGGGAACCATAAAGGATCTTAAGCAGAGAAGTGACT
TTCTTAATTTTGAACCTATCCTGGTGTTCTCATAGATTAGAGGAGAGAGATTTAGGAGTGAGGGATCAAG
CAAGAAGGTGGCTCCACATTGTTTTCCATAGTAGTTGTACTAGTTTACATTCCCACCAGCAGTATAGAAA
TGTTCGCTTTTCACTACATCCACACCAACGTCTATTATTTTTTGATTTTTTGAAAATGGCCATTCTTGTG
GGAGTAAGGTGGTATTGCATTGTGGTTTTGAGTTGCATTTCCCTGATCTTTGGTGATGTTGAGTATTTTT
TCATATGTTTGTTGGCCACTTTGTATCTTCTTTTGAGAACTGTCTATTCATGTCCTTAGCCCACTTTTTG
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TTAGATGTATAGATTATGTCTCCTTCTCTGTGGGTTGTTTGTTTACTCTGCTGCTGCTCCTTTTGTGCAA
AAGCTCTTTAGTTTAACTAAGTCCCACTTATTTATCTTTGTTTTTGTTGCATTTGCTTTTGGGTTTTTGG
TCATAAAATCCTTGCCTAAGCCCATGTCTAGAAGGGTTTTTCTGACGTTAACTTCTAGAATTTTATGGTT
CCAGGTCTTAGATTTAAGTCCTTGATCCATCTTGAGTTGATTTTTGTGTAAAGTGAGAGATGAAGATCCA

GTTGCATTCTCCTACATGTGGTTTGGCAATTATCCCAGTACCATTTGTTGAATAGGGTGTCCTTTCCCCA
CTTTATGTTTTTGTTGGCTTTGGCAAAGAGCAGTTGGCTGTAAGTATTTGGGTTTATTTCTCGGTTCTCT
ACTCTGTTCCTTTGGTCTACATGCCTATTTTTATACCAGTACCATGCTGTTTCGGTGACTATGGCCTTAT
AGTATAGTTTGAAATCAGGTAATGTGATGCCTCCAGATTTGTTCTTTTTGCTTAGTCTTACTTTGGCTAT
GTGGGCTCTTTTTTGGTTCCATATTAATTTAGGATTTTTTTCTAGTTCTGTGAAGAATGATGGTGGTA
TTTTGATGGGAATTGCATTGAAGTTGTAGATTGCTTTTGGCAGTATGATCATTTTCACAATATTGATTCT
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TTTGTAGTTTTCTTTGTAGAGGTCCTTCACCTTCTTGGTTAGTTTTTGTTTTTTTTGGTTTTTTTTTTTT
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GCAGAGCTACTGATTTGTGTACATTAATTTTGTATCCTGAAACTCTGCTGAATTCATTAATCAGTTCTAG
GAGCTTTTTGGGGGAGTCTTTAGGGTTTTCTAGTTATAAAATCATATCATCAGCAAACAGCGACAGTTTG
AATTCCTCTTTACTAATTTGGATGTCCTTTATTTCTTTCTCTTGTCTGCTCCGGCTAGGACTTCTGGTAC
TGTGTTGAATAGTGAGAGTGGGCATCTTTGTTTTGTTCCAGTTCTCAGAGGAAATGCTTTCAACTTTTCC
CCATTCAGTATTATGTTGGCTGTGGGTTTATCATAGATGCCTTTTATTACAGTGAGGTACCTTGTATACC
GATTTTGCTGAAGGTTTTAATCATAAAGGGATGCTGGATTTTGTCAAATGCTTTTTCTGTATCTATTGCG
ATTATTGCGATGGTCATGCGATTTTTGTTTTTAATTTTGTTCAGGTGGTGTGTCACATTTATTGACTTGC
ATATGTTAAACCATCCCTGCATCCCTGGTATGAAACCCACTTGATCATTGTGGATTATCTTTTTGATATG
CTGTTTGATTTGGTTAGCTAGTATTTCGTTAAGGATATTTTTTTGAGATGGAGTTTTGCTCTTGTTGCCC
AGGCTGGAGTGTAGTGGCACTGCAACTTCCACTTTCTGGTTTCCAGCGATTCTCCTGCCTCAGCTCCCTG
AGTCGCTAGGATTACAGGCACCTGCCACCACACCCAGCTAATTTTTGTATTTTTAGTAGAGATAGGGTTT
CGCTATGTTGGCCAGGCGGGTCTTGAACTCCTGACCTCGTGATCCACCTGCCTTGGCCTCTCAAAGGACT
CTCAAAGTGTTGGGATTACAGGCGTGAGCCACAGCGCCCGGCCAGATTTTTGCATCTATGTTCATTAGGA
ATATTGGCCTGTAGGTTTCTTTTTTTGTTTTGTTCTTTCTTGGTTTTGGTACAAGGGTGATACTGGCTTC
ATCGAATGATTTAGGGAGGATTCCCTCTTTCTTCATCTTGTGGAATAGTGTCAATAGGATTGGTACCAAT
TCTTCTTTGAGTGTCTGGTAGAATTCAGCTGTGAATTCATCTGGTCCTGGACTTTTTGTGTTGTTGGTAA
TTTTTAAATTACCATTTCAATCTTGCTGCTTGTTATTGGCCTGTTCAGGATTTCTAATTCTTCCTGACTT
AAGCTAGGAGGTTTGTATCTTTCCAGGAATTTACCTATCTCTTCTAGGTTTTCTAGTTTATGTGTGTAAA
GGTGTTCATAGTAGCCTTGAATGATCTTTTGTATTTCTGTGGGGTTGGTTGTAATATCTCCTGTTTGTTT
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TTATCTTTTCAAATAACCAGCTTCTTTTTGTTTCATTTATCTTTTGTATTTTTTTTTCAATTTCCTTTAG
CTCTGCTCTGATCTTGGTATTTTCTTTCTTCTGCTGGCTTTGGGTTTCGTTTGTTTTTATTTCTGTAGTT
CCTTGATTTGTGACCTTAGATTGTCTATTTGTGCTCTTTCAGAGTTTTTGAGTAGGCATTTAAGGCTGTG
AACTTTCCTCTTCGCATTGCTTTTGCTGTATCCCAGAGGTTTGGATGGTTGTGTCACTATTATTGTTCAA
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GTTTACGTCAATTAAGAATTTAGAAAGAATTTAGAATCCTGTGTAAAATAAATTTCCTTTTATTTTACCT
TAATTCATGCATTCTCTGATTATCTTCCATGCTTTATGTAGATCCAAGTTTCTGACTTATATCACCTTCC
TCTTGCTTGAAGAACATCTTTTAACATATTCTGCAGGGCAAGTCAGCTGGTGATGAATTCTCTGAATTTT
TGTCTGATTTTTTTTTAATATTTCCTTCACTTTTGAAGGATAATTTCCCTGCATCTAGAATTCTAAATTG
GTCACTTTTTTCAACATTTTATATATTTTACTTCACTTTCTTTATTAATGTACGGTTTCTGAAGAGAAAT
CTGCTGTATTTCATCCTGTTCTCTATGGTTAGGTGCTTCCCTGCCCTGGCTCTGGCTTTTTCAAGATTTT
CTCCCTGTCTTTGGTTTTTCTACAGTTTGAATACAATATGCCTAGGTGTTGTTTGTTTTGTTTTTTTGTA
AGGAGTGGCATGTATTTATCTTCTTGATACTCCCTGAGCTTCCTGGATCTGTGGTTTGGTGTCTGTCATT
AATTTTGAAAAGTTCTCAGCCATTACTACCTCAAATATTTCTTCTTCGCCTTTCTTTTTTTTTCTTTCTG
GTATTCCAATTATGCATATGCTTGTTATACCTTTTGCTTTTTCATTCTTTTGATTCTTTACATTTCAGTT
GGGGACGTTTCTGTTGACTTATCTTTCAGCTCACTGATTATTTCCTTGGCCGTGTTGAATCAATTGATTA
GTCCTCAAAGACATTTTTCATTTCTGTTACACCATTTTTACATTTCTAGCATTTGCTTTTGATTCTTTCT
TAAAATTTCTATCTTTCTGCTTATATTACCCATCTTTTATTGTATGTTGTCTTCTTTTTCCATTAGAGCC
CTCAAACTCTTTTTTTTTATTATACTTTAAGTTTTAGGGTACATGTGCACATTGTGCAGGTTAGTTACAT
ATGTATACATGTGCCATGCTTGTGCGCTGCACCCACTAACTCGTCATCTAGCATTAGGTATATCTCCCAA
TGCTATCCCTCCCCCCTCCCCCCACCCCACAACACTCCCCAGAGTGTGATATTCCCCTTCCTGTGTCCAT
GTGATCTCATTGTTCAGTTCCCACCTATGAGTGAGAATATGCGGTGTTTGGTTTTTTGTTCTTGCGATAG
TTTACTGAGAATGATGATTTCCAATTTCATCCATGTCCCTACAAAGGACATGAACTCATCATTTTTTATG
GCTGCATAGTATTCCGTGGTGTATATGTGCCACATTTTCTTAATCCAGTCTATCATTGTTGGACATTTGG
GTTGGTTCCAAGTCTTTGCTATTGTGAATAATGCCGCAATAAACATACGTGTGCATGTGTCTTTATAGCA
GCATGATTTATAGTCATTTGGGCATATACCCAGTAATGGGATAGCTGGGTCAAATGGTATTTCTAGTTCT
AGATCCCTGAGGAATCGCCACACTGACTTCCACAATGGTTGAACTAGTTTACAGTCCCACCAACAGTGTA
AAAGTCTTCCTATTTCTCCACATCCTCTCCAGCACCTGTTGTTTCCTGACTTTTTAATGATTGCCATTCT
AACTGGTGTGAGATGGTATCTCATTGTGGTTTTGATTTGCATTTCTCTGATGGCTAGTGATGATGAGCAT
TTTTTCATGTGTCTGTTGGCTGCATAAATGTCTTCTTTTGAGAAGTGTCTGTTCATGTCCTTTGCCCACT
TTTTGATGGGGTTGTTTGTTTTTTTCTTGTAAATTTGTTTGAGTTCATTGTAGATTCTGGATATTAGCCC
TTTGTCAGATGAGTAGGTTGCGAAAATTTTCTCCCATTTTGTAGGTTGCCTGTTCACTCTGATGGTAGTT
TCTTTTGCTGTGCAGAAGCTCTTTAGTTTAATTAGATCCCATTTGTCAATTTTGGCTTTTGTTGCCATTG
CTTTTGGTGTTTTGGACATGAAGTCCTTGCCCATGCCTATGTCCTGAATGGTAATGCCTAGGTTTTCTTC
TAGGGTTTTTATGGTTTTAGGTCTAACGTTTAAATCTTTAATCCATCTTGAATTGATTTTTGTATAAGGT
GTAAGGAAGGGATCCAGTTTCAGCTTTCTACATATGGCTAGCCAGTTTTCCCAGCACCATTTATTAAATA
GGGAATCCTTTCCCTGTTGCTTGTTTTTCTCAGGTTTGTCAAAGATCAGATAGTTGTAGGTATGCGGCGT
TATTTCTGAGGGCTCTGTTCTGTTCCATTGATCTATATCTCTGTTTTGGTACCAGTACCATGCTGTTTTG
GTTACTGTAGCCTTGTAGTATAGTTTGAAGTCAGGTAGTGTGATGCCTCCAGCTTTGTTCTTTTTGGCTTA
GGATTGACTTGGCGATGTGGGCTCTTTTTTGGTTCCATATGAACTTTAAAGTAGTTTTTTCCAATTCTGT
GAAGAAAGATATTGGTAGCTTGATGGGGATGGCATTGAATCTGTAAATTACCTTGGGCAGTATGGCCATT
TTCACGATATTGATTCTTCCTACCCATGAGCATGGAATGTTCTTCCGTTTGTTTGTATCCTCTTTTATTT
CATTGAGCAGTGGTTTGTAGTTCTCCTTGAAGAGGTCCTTCACATCCCTTGTAAGTTGTATTCCTAGGTA
TTTTATTCTCTTTGAAGCAATTGTGAATGGGAGTTCACTCATGATTTGGCTCTCTGTTTGTCTGTTGTTG
GTGTATAAGAATGCTTGTGATTTTTGTACATTGATTTTGTATCCTGAGACTTTGCTGAAGTTGCTTATCA
GCTGAAGGAGATTTTGGGCTGAGACAATGGGGTTTTCTAGATATACAATCATGTCGTCTGCAAACAGGGA
CAATTTGACTTCCTCTTTTCCTAATTGAATACCCTTTATTTCCTTCTCCTGCCTAATTGCCCTGGCCAGA
ACTTCCAACACTATGTTGAATAGGAGCGGTGAGAGAGGGCATCCCTGTCTTGTGCCAGTTTTCAAAGGGA
ATGCTTCCAGTTTTTGCCCATTCAGTATGATATTGGCTGTGGGTTTGTCATAGATAGCTCTTATTATTTT
GACATACGTCCCATCAATACCTAATTTATTGGGAGTTTTTAGCATGAAGAGTTGTTGAATTTTGTCAAAG
GCTTTTTCTGCATCTATTGAGATAATCATGTGGTTTTTGTCTTTGTAGAGCCCTCAAATTCCTAATCACA
ATTGTTTATCTCTTTCCTGACATTCCACATCCAATCCATCAGCATGTCTTATTGGCTTTACTTTCAAAAT
AAATTAAACTCAGCCACTTCTCAGCATTTTTAAAATCACCCTAATACAAACCCCCTGCTACCTCATCAAC
TGCAATGGCTTCCTAACTTATTTTGTAACTTTTGATCTTTGAGTTCTTCCAAGAGCCAAGAGTTCTTCCA
AAGCTATAAACCCTATCATTGGCACTCCTCTGCTCTATGGAAAGCAGTGGCTTCTCATCTCTTTCAGAGT
ATAATGCAAAGCTCTCACCTTAGCTGGCATGGCCCTGTGGGATTGGCCTCCCTTGTCTTACTTTTTCCTT
GTTCAGGCTGCTGTGACCTCTCTGGTCTTTGGCTCTTACTAGAAACCTTTGAACCCGTTTCCTTCCCAGT
GTCAGTATTTGTGTGTTGTTCGTTCACCCCTTCTCACTTCATTCTGGTTTCTACAGCACAGAGAAGTAGTA
GTCCCTGATCTAAACACCCTCTCCACCTGCTTTCCACTTTGTTTTTTCCCCTAGCACTTACCATTATCAG
ATATCATATATTTATTTGTTTATTGTCTAACTTCCTCACAAAAATATGACGTTGTGAGGATAGGGATTTG
GCTTTTTGCCCCAGAGCAGTGCCTGACTCTCAATAACTTTGTTGTATTAAGTGAATGAATAAAATAAAAT
TAAAATTGATTCAAAGTGTATGAGCATGTGTACATTTTACATAAGTGATACATGACATTCTTCCATTCCT
TGGGGGCTCTTTTAACCATTCTCAACCAGTTGTAGTACCTTTAAAAAAATCATGATGAAGATGATTTTGAG
AGCTAATTTTGGTAGGAGACAGCAGTTTTAGCCTGTCCGCTCCATGTGCAGAATAATAGCCTATTTTATT
ACATCTGATATTCAAGCACTAGAATCTATCAATAGGTAAATAATTTCCAAAAATAAAAGCATCAGTGGGA
AAACAGGGAAATTATTTTTAAAAAAGAATTTCTAGACCAGGATGTGTGCAATTTGTAATCTCTAATAAGA
AACGTTATAGCTGATAATTCCAGCAATTACAGAATCATGATCATATCCATAATGGATCAGTAGAGGCTCT
GGCTTATATAATAGCTTGCCCTCTCAGGATTCTAGAGCCCCATATGTAAACACAGAACACATTTATATTG
ATTGACAGTGCATGTAGGTTTCTACAGATTGTGCCAGTCAGTGTTTTCTAAGGCAGTTATGCCATGGTAA
TTAAAATTATGGGCTCTGAAATCAGCCTGCCTGGGTTCAAACCCCAGCTTCATGTGTCAGCTTCCTTGGC
TGTAATAAGGAATACTAATAGCACCTGCCTTGTGGCTTTGAAAATTACATGATGTAACTTTGTCAAGAGC
TTAGATGAGCACTTGGGATATGGCGAGTGCTCAATAAATGTTAGTTTACCATCATCATCATCATTATTAT

FIGURE 1, page 59 of 93

TATTACTGATTGCAAGCAAGACAAACTGGTTCTCACTTCAGCAGAAAAAGAAATTACTGAAGTAATTTTG
GTTAGATCACAGATTTAACGTGAAGGATGAATAACCAGACTTGGAAAACAGGTGGAAACCAAGAGGCAGT
CAGCATGGCATAGCAGCCAGCACTTCACCAGTGTGGTGCCTTGGGGGCAGCCTGGCAGGAGCCACTGCCT
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CAGTAATTGTCCTTGTAGCTTTTGTGATGGAAAGCAAGTCCTGACACCCACCAACTCACATACTAGGGAA
TTCACCAAATGTAGGACGGCAGCTAAGATGCTGGGAAACCAAGAATTAACAAATGAGTATTACACCAATT
AGTTAATTCATTACAGATTTCAATATTTTCCAAAAAACATCCTACAAAGAACAGCTCACTTTAATATACT
CCAACAAATGATGAAATCTCTCCTTGGTCATCAGCTTTTCTAAATTTCTGTAACTTTAGGTGATTCTGAA
TTTCTTAGTGATTCTGAACTTCTAGAAGATTCTGAAACAGAACAGTCTTACTTTGGGATGTATTCAAATC
CTAGAGATCAGTCACATCAATCTGTGCCCTTTTTCATTATGTAACATGAAACAGGAGGACCTTTCCAACT
TGCCTTGGGAACCTGCTCCTACAACAGGGTATATTATCACATTTAATAAAGAAAGAGTAATATTTGCATT
GTGACCCTTCATCTGAGGTCATCGGGACTGTGCTGTCCTCCCAAGCTCCACTGTAAAGGGATAGACAACA
ACCTTGTCTCCCAGTCATTGTAATCTGTATCAGAGAGCATCATTAGATGAATGAAGATGGAAATGTTCTC
ACGGTCAGCAGGTGGGGAAGGCAAGACTTGCTGATTGGAAGCAATGAACCATAGTTCATTCTAAGGCTTG
GGGAGAGCAACTTTGAGGAAATGAGGCCCCTAAACTTGCCATGTAGGAGAAGTTGGGGGGTGGTAAATTG
GGCACCCTTTATCTACTAAACGTAATCTTTACTTCCCCACCCTCTAATTTTTCTCAGTTGGGCTTGAAAT
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AGAAGAAGAAACTAAGAATTTCAAATTGACAGTTTGTTAATGAGAAAAGACAAGGTTAAAGGATTTTGTT
AAACAGATGACCAAAATAATTATTGGAAACTTCTGCTTCTGGCCAAGGTGGAATAATAAGGGCTACATTT
ACCTTCCCACCAGAAAATATAATAACAAACAAAAACTGGACAAAACACTGGACATGACACTGTTGTCTTT
AAACCTTGGACATCAATCAGTGCAGGATGTTATTTTGTAAGAAAGGGAAAAAAATTGGGGTGAGCCTTCT
GATTGTTTCCAGACTGGAGAGAAGTTTCAGGCCACAGCAAGTGGGGAGGAACCTAGGTGTAAGTATATGT
ATAAGGTAGCACATCATAGTGGCCAAATGAATGGCACAGGAAAGAAAAACTACAAGAACAGAGGAGGTAG
GGCCACAAAACTAGAGTGGGGTCCAAGATTCACTATGGATAAAATGGGGTGTTAATTTGGTTTTCAAGGC
CAATACAAGAGGAGGCATAGAAAAAGAACAAGGTGGTGTTGGGAAGTAGTATAAAAAGGGGCACAGGCTT
ATCCTTGTTTTATAAAAAACAAAGGTTTTTGGAAGGGATTTGTAGAGATAAGTTTGAAAAGTAGTTTGAG
ACTATGTGTGGAAATTCATGAATCTTAGAGTTTGATTTTATTCAGGAGATCAGTAGCTTTTAAAATGTAA
AATAAAACCAGTAAACTCTATCTAAAATAAATTCTTCCCCTAATCCCAATATAAAAAATACATATAAAAG
CGTAGCTGCTCTAGACAAAATGGCGGGTATGAGATGACCAGAAACCTCAACAGCACTACCTCTGGTAGCC
CCATAGAACTGCCAAGAGTTTTCAGAGTATAGTTAATTCCTGCTGACGGCTAAGGCAGTCATTGAGTGAT
TGGAAAGAAGACGGAAGATAGACAAGATCAGTTAATTGGGTTGGAGGGAAGACTGAAGATAGGCAAGGTG
ACAAATTAGGAACTGTTGCAATGATCTAGGCAAGAAGGAACCTATGAACTAGGAGGGAGGCTTAAAGACA
GCAAGGAGGGAACTATAGGCAGGGACATGTGAGGAAATGCTTAGTAGTTAAGGTGAGTTTGTAGGTATGA
AAGGAGAGAAGGAAAGAACATTAAGTAGCATTAAGTGAACCAGATAATTTATAGCTCCTTGACCTGAAAC
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CATGATATAATCATCTTACCAATGCTTTACAGTCAATGACATTGTGGTACAGAGACTTTGGAGGCAGATA
GACCTCGATTGTAACCTCTGTGCTGCCCGTGGTATGACCTTGAGCATGGTAGTTAATCTGAACTTCTTTC
TTTTCTGTTAAATTGGGGACAATGACAGTACTTAACCTTATAGTACTTGAAGGGAGAGTGTTAGAATTGA
TACTGGGGAGTCTCTCCACAGAAAGTTGTATTAGTTATTGTCTTTATTTCATTCTTAATGAATTAGCACT
CCCGTTTTCTTTAACATGTTGAATTTAAAACCTCTTAGTGTATTTCTTTGTCTTGCCTTTTAATACCCCA
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CATGGGAAACTGGAGAAATAACTTTACTGATATTATACTAGTTTTTTTCTGGAAGCATAGCATATTAAG
AAAACTCATTTCAATGAAAGAAAATTTAAAAATTAGAGTGCATTAGAAGCATAATCCAATGAATTCTATT
CCTAATGAATACTCAGGCAGTATGTTAACTTTTTCTGAGATACAATAGCCAAGCCAAAGAATTTAAAGAA
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CTTTGAAGAGATTCCTTAGGGCTCACCTCCCCTGGAGAGTGCCCTCTGTACCATCTCTCTCCCTTTCCTC
CTCATTCCTATTGCCTGAGTTTATTGTTTTAATAAATTCCCATAAGTTAACACCTCCTAGGGTGGATTAG
AATCATTCAAATCCACATTGATTGTTACTAAGTAGAAATTTTATACTGAGCCTTTCTAAATCCTTACAAC
AACGTGACGAGGATATTATAGTTGCTTTAACCCAAGGAGATGAAATTCAAACTGGTGGCATTGCACACTT
ACAGTGGGCTTGCAGGATGAAAGAGAGCTTGGTATCTCGATCCCTTATACAAAACAGGTGGGTCTTGTTA
GAAAAATTCTTCAATAATTGTTAAGGTTAAAATTTTGAAAAGTGGTTCAAAGAAATTTGCTTTGATGCAA
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TCTATTGTGCTGTTGAATATACTGCTCAACCATTCTGGAAAATGGCATGTTCATGTATGAATGACAATGT
ATCTTGTGTGTATGGCATTCCAAGCCAACATGTTGGTCCCTGCAAGTAAACTTCTTGACTGTCAAGAGGC
TGCCTGTTTAATATTTGCATGATCTAAACTAATTGTTTCCTTTGTTTTTTTCCTCTGCTTTATGAGCTGG
TAGTTTGACCTTTTGGCTTTTCCCCTGAGAGTTAACAAAAGTTAGACAGTTGGGGGGTGAACTTAAGTAA
AATCCATATCACTCTATGTTGCTGCTCTACTAACAATTCAAGAAAATGTCTTGGTAGAAAGCAAGGAATG
AGTTTTAAATTTTCTCTTTGAATTTCAATTATCCATGCCACTCCTGTGGTCCACCATTCTATATAATTAA
GAATAAGCTGTATGTTCCATAGTGACACAGGCTGTTATTTCTGATTTGCAGTTTTCACTTAACCTAGGGT
AAAATTGAAATAGAAGTCGCATCCTTTTTTTTTTACCTTCTTCCACTCAATTCTAGTTAGATATTTTTGA
ACTTCTATAAAATGTCTATGCAATATTATCACCAATAATGTGCAAAATTACTACTCCCATGTAGAAGAGG
ATCCATTCTTCATTGAACCATACCCTTGGGATCCTATCACATGCAGTTGGCCATATAATATTTTATATTA
TTGTTTTTTTGTTTTGTTTGTTAAGTTTGTACCTACATAATGGATTAAATTCAAAATCTCTGTTTAACTG
AAACAAAATCTGTTTAACTGAAGCAAAAAAACAAAATCTCTGTTTTTTGTTTGTACAAAACAAAAAACAA
TAATATTTTTGTTTTGTTTGTATACTTCATAGGGACTTTGGAATTTGGAAAATATCGTTCATTTAGGGTA
TATATATTAGTCCATTTTCATACTGCTATAAAGAAATACTTGAGACTGGGTAATTTATAAAGAAAAATAG
GCTTAATGAACTCACAGTTCCACATGGCTGGGGAGGCCTCACAGTCATGGCAGAAGGTGAAGGGGAAGCA
AAGGCATGTCTTATATGGCAGCAGGCAAGAGAGTATATGCAAGGGAACTGCCCTGTATGAAACCATCAGA
TCTCATGAGACTTATTTACTATCATGAGAACAGCACAGGAAAAACCTGCCCCCATGATTCAGTTACCTCC

CACTGAGTCCCTCCCACATGTGGGGATTATGGGAACTACAATTCAAGATGAGATTTGGATGGGGACACAG
CCAAACCATATCAGTACATTAAAGAAAATATTTGTTAGCGCTAAGTGAATCTACTTTCACCTACTTGATT
ATTTGATGATTTTATAAATAGTCATCTCTTTCCTCATCTTTCCAGTCGTATTTTGTTGTTCCAAAGCCAA
AACCTGTGTGTCTTGTATTCAACAACCTGAATCATACAGTTGTGAGACGTAAATGGGTGTGGTGGTTCCA
CTTACTTCTTTACATAGTACTACAACTAAGCCATCTAAGTAGTCTGCTCCTAAATTCCTCCAAGAAGGGA
AATATCATGATTTGATTTAAATGTGACATCCTTTCTTAGAGAAGTTTTCTTTGTCTCCTTCTTCCCCAGT
CACTTCCTCCCATCCACTGTGCTTTCGGCAGTTCATTCGTTCATTAATTCATTCAACGAATATTGAATAA
CTTTTGATCAATGTCTTCCTCCCTCCAAGCTGAAAACTTGATGGAGGGTAACATGATCTGTCTTTGTTTA
CCACTGCATCTTCCGTGAATATACATTGTAAGTATTGAACGGATTTTTACTAAATGAACAAATACTTTGA
TAAAATATTTTTGATTACTGCCAATATCAGTTTCTGAATTGATTCTAAAATTCTTCTGCTGGAAAGTAGA
TTAGCGTTAGTATGACTGCTGAAGCCTTTTAAAGTGGGTGGTAATACTACGTTTCGTTTTGTTTCATTAA
CCTAAGTGCTGTTCTTTGGAATCTTTTTAAAGTAAGATAAATTACATTCATGAAAGAAGCATATTATTTT
TAAAGTACTTTATTTTGGAAAGGTAAAATGCTTGTGTAGTTATAATTTGGTTACTCTTGATTTCACCTTA
GGAAAAACAATATCACCTTCTAACCATTTCTTTTTTAGTCAAATCTCTTGCTTCTATTTCTCTCTGTAGA
TCCGCTATTAAAGACTGTAATCACTGCTGCATCTTTCCTGTAAGGCTTGATCGCATTGTTAATTTCTTTC
TAAACTTGTAGAGTAGGTGTATAAATCGTATTTGGGTAATACACTGACTAATACTGAAGAACCAGGCATT
TTCTTACCCCAGTCCTCACACGAAGTAGGGAAATACAAGTCAGAACTTATCTTCTCAAAACTCTGACCTC
AGAATTTCCTGAGAAATCTGAACCTAAAAAGATTCTTTGCTTTTGACATTTTTTCTCTGGTGTCCACCGC
AAGGCTCTTGCTCTTACATTTTTTTTTTTTTTTCTAATGTTTCAAATAGAAGATGGTAGAGTCATATAGTA
CAAGCTCAGCATCGGAGGGGCTACTGGAGGTCAACTAGTGCAAATGCTTTCTGAATAATGGAATCCTTTG
GGAATACCCCCTTGAAAGTCTTCATCTAGCCTCTTCTTGGAAACCCTCAGTGATACCCCTCATCGTCTCC
TATGATGGCAGCTTCTATCTTTGTCGTCAGCTCTGACTATTACAAACTGCTTCCTTACATTGAGCTGTAA
CTAACTAAAAAGTTTCCACACCCTGCTTCTATTTTAGCCTTTGGGCTCATAAAGAACAAGTTGAACCCGT
CTTATGCAGAACAACCCATCTACGGGAGATGCTCAGGTTTCCTCCATGTTTTCCTTTCTCTAGGCTAACC
CTTCGTTGTTCCTCACTTACTCACTATATAACCTGATTTCATGTCTCCTTACCCTTCTTGTTACTCTAAC
TTGAGTAGGCTAGTTTCAGGATCCAGCAATAAGTGTGATACATCAGGTATGCTCTGATGAGTTGAGAGTA
GAGTGGACATAGCATCTCCCTTAATTCAGATATTGTGATCTAATTGGCAAATCTGGCAATAAAAGTTGAA
ATGCCTGATCCAGGACAATGGCTGGTCAGGTGCCATTGTTCTCATCTTTTACTTTTAGGTGTCCCTCAAT
TTGTTAAGTTAGTACCTACGTAATGTCCTGAAACTTGTTAAGTTTGTACCTACATAATGGATTAAATTCA
AAATCTCTGTTTAACTGAAAACAAAAGCAAACTTCTTTTCAGAGCCAGAATCTGGAATCATACGTAACAG
AGAATGATATTGTACAAGTTGCTTCATCTCTTTAAGTAACGGTTTCTCAAACTTACAAGATTATTGTGAG
AACTAAATTAGTTCTAAAGTGCTTCCATGTAAAGTGTATGTAAATGCTTAAAATATATAGTAAGTGCTGA
ATGCATATTAGAAATAATAATAATCTTTATTATAATTTTTACTATTTCATGAGAAGTACTTATTTTAATA
CTGAGCAAATAGGAAGAGTTCATGGCTTCTCTATGTTTTTGAAGTGTCATTTAATATATTATATATATAA
AACATATATATATTTCAGTCACACATTTGTCCAAATACCTTGACAAATTAAAACAAAATAAGACAAAATT
CTCACGCTAGTTATTTGTTATAAAGTAATAGAACAAGTGATATGTTATAAAGAGCATTTATTTCTCATGT
CTTTGATATTAAAAATAGTTGTATTAACTTTTTATCAAAACGATTGCTTCCTTCATATAAATCTAAGAAT
TATGCTGTCTGATAAATATTGGAGAGATTAACTTCTTTGAAAATATAGAAGCTTTTTGTCTTTTTAAAAT
AGTTGTTTTTTTGCAGATGTTAATACATTTCAGCAGTACAGTATGGCCTTTTTCAGGTTAAGGTGCTGAG
CCCAAACCTCAAAGAATCACTGCAAAAAGATTGGATCCCCCCTCTTCACCCCATTTCGTAATTTAGTTAG
TGAGAACCACAACTGGCTAAACCTTTGTGGGGGGCCGGGCACTGTGGCTCATGCCTATAATCCCAGCACT
TTGGGAGGCCGAGGCAGGCAGATCACAAGGTCAGGAAATCGAGACCATCCTGGCTAACACGGCGAAACCC
CGTCTCTACTAAAAATACAAAAAATTAGCCGGGCATGGTGGCAGGTGCCTGTAGTCCCAGCTACTCAGGA
GGCTGAGGCAGGAGAATGGCGTGAACCTGGGAGGCGGGGCTTGCAGTGGGCCGAGATCCCGCCACTGCAC
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CCACCTTTGGGGGGAAATTATCAAATAAAACAAACTCTTTTTAGAATTTTACAACTTTTATGTTAGGAAA
AAACAAATACATTTGTGAAAAGCTTAAAATCCAGTAAATGACTTGAGGGACTTGGGGCAATCCTAGGGTG
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AGCAAGTCATTCTTATTTAGTCTTGCCCATTAAGAAGTCTACTTGGACTAAATGCTTTTAAAAATGCCCT
TTTAATTTACTATTAAAAGAATATTCCTAGCAGAAGTAGTCTTGGATGCTAAATTCTATTTTAAGAATAA
CTAAAATTAGAATTCTGTTCTTTTTATAACACCTGTTACACACACACCCCTACCTAGTGTGTCGGAATCA
GTTTGTATGGGCTCACCAAAGCCTACTGTTCAATTTTCAGGAGTTTTGTAAGCCATTTGATGTCAGACAA
GTGGCCTGAAGTTTGTTATGGTGGTGGTATTTACACCATGAAAATTGGCATGTTATGGTGGTAGTATTTA
CACCATGAAAACTGCTACAAATAGAAATCTTTTTCTTCTTCTCTTGGAGAGCCACTTGTTGAACACTTAC
CAGCTCACCTGTGCTTGAAAGTATTTCTTCAAATAAAATGAAAGCTGGTTAGCTTTGAAAATTTTTTGTA
TAAAAGTTTACACGGGAAAAAAATAAACTAATTTTTTTTTTCCACCTGTGTTTTCAGGGATACGAAAAGA
CCGAAGAGGAGGGAGAATGTTGAAACACAAGCGCCAGAGAGATGATGGGGAGGGCAGGGGTGAAGTGGGG
TCTGCTGGAGACATGAGAGCTGCCAACCTTTGGCCAAGCCCGCTCATGATCAAACGCTCTAAGAAGAACA
GCCTGGCCTTGTCCCTGACGGCCGACCAGATGGTCAGTGCCTTGTTGGATGCTGAGCCCCCCATACTCTA
TTCCGAGTATGATCCTACCAGACCCTTCAGTGAAGCTTCGATGATGGGCTTACTGACCAACCTGGCAGAC
AGGGAGCTGGTTCACATGATCAACTGGGCGAAGAGGGTGCCAGGTAAGAATGCGAAGCGCAGCTTTTAAG
AGTCAATAGCTTTTCAAGAACTTGTTGTGATGTCATGGGAGAAATAGTGGGGGAAAAAGAAGCAATAACA
TGTTATGTAATTGGTTTCAAGGTTACAGGAGATGTGTTCATTTTCAGTATCAATACACTGTAATTTTCCA
GGAGATTAGGAAATAATATTTTTAAATCAGAATCTAGAAGACTGAAATTCTTAAATTGACATAATTTATT
TTTAACCCATCTCATTTACCAAAAAGATTTAGGGTGGACACTACATGGTAAAACTATTTAATAGTGTATG
TTCACAGTAGCAGAAACTTTTAACACTAAATGAACTACAAAAGTTTGTAATATTAATGACCTTTGTTGAA
AACATCTCAATTATTAATCAAACGATTTTATCTTAAAAAGATTTTTAAGATTCGGTGTGGTGGCTCGTGC
CTGTAATCCTAGCACTTTTTGGGGCTGAGGTGGGAGGATTGCTTGAGCCCAGGAGCTTGAGGCCATCCGG
GGCAACGTGGCGAAACCCTGTCTCTACAACAAATTTTTAAAAATTAGCTGGATGCAGTGGCACACACCTG
TGGTCCCAGTTATGGGGGAGGCCGAGGTGAGAGGATGGCTTGAGTCCAGGAGGTCAAAGCTACAGTGAAC
CATGTTTGTGTGGAGTGCCACTGCACTCCAGCCCAGGTGACAGAGCAAGACCGTGTCATAAAAAATAAAC
CACACACAAAAAGAGAAAGATCTTTATGGATTAAAAAGATAATAATAAGTGTATTTACTGAATGCCAATT

FIGURE 1, page 61 of 93

ATTTATCCAACCTGGTGTATGCTTAGTATTTTAGGAGAAAGAGAAAGGCAATGGAAAAATAAATTAAGGT
ATCATCCCTGAAAGAAACTTTTAGAAAGACACAGTGGCTGAAGTGATACCTTGTTCCTTCAGTTGATTCT
CTCAGAACTGGTGTTCTGGTAAAATTGGACTGTTACTCCTGTTATTCAGGGAGAAGAACTCAAGTTTGTA
TGGCAACAAGACTAGAAAATGACTTTCTCCCTGCCCCAGTGTATTCGTTCAGGAGCTAATGTAGATAAAC
CGAGGCAAGAAGAAGCTAAATTTTTTTTCTGGGCTTATAGGTTAAATGAGTGATAGATTTAGTTGGAGGT
TTTCTCATTTGGTTTCTTTTAATAGATGAAATTAATTGTTTCCTATGAAGCATGAAATGTTTTATATGAA
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GTCTGGCCTTAGAGAATCTTACATGTATTTGCATCTATCAGTATATAAACATGTGGGCCGTAGAATAAGG
AGCCAGCAGTACCAGAACCCAGCCTTGTTAGAGGCCACCATTTTGGTGGTTGAGTGGTTATTAGTTTACA
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GTCATCTTCAGAATGAAAAGTTTTCTTGAGTACCTACATATTTTAGCATTTTCATATGAAGCAGATACAT
TATAAGTTAATTGTTGGAATCTAATTGTAATATGGCTGTAAGTTTTTTCTTTATATTTGTTATTGCCTTG
TTCTTATATTATAGGGAAAGAGAAACAAACAAACAAGCAAAGAAACTAATGGTCATATATTTGAGAGCCA
ACTCTTGGTTGCTGTTCAGTTTTATTTTCCTGTAAACATATATTTTCCCTTATGAAATCTTGGGAATATT
AGCTCTGGAGCACTGCTGAACTCAAGTACAGACATTTTCATGTGTATCAGTAGATTCCCATCATGACATT
TTTATAATAATGTTGAAGAGCATTTTAAACAACTGGAATTAAGCTCAAATACATTACCAGTGGTTGAAGA
ATTCACATCAATAATCTTCTGAATTTAGGAATAAAATGGAGAAGTCAAGGAAAGCCAAATATTATACACA
GGCTAGCAATAGTTAAAATACAATTATTAAAGCCAGAGCTAGACAAAATTATGGCAATGAGATGTGTAAC
AAAACCACTCTGTAACTTCATCATGTTCGTTTAAAAGACCTGAATGATTCCAAAATCCTTAGACCAATAA
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TTTGTGTGTGTTCCATGGGAATACAGCTGTTGTAAATCAAAGGCCTACTTGCCTGACCAAGCAGAATAAA
AATAGTCATTGATTTTAAAGAGACTAAAAGTGAGGGAAGAAAAAAGTCTTCTGCAAAAGCTCTACAGATG
GTTGTCAAACTTTTCAGAAAAAATAGACAAAGCAACATTTTGAAAAGGATTTATATCTTTTATATATTCAA
ATACCATCTGTTATTTAAAAAACATAGCCCACACTGAATATCTGATATAGACAATATAACGTTTATGAGA
TAATAGTTTGAGAATGACAATAATAATAGTAAGTTTTAAAAGAGGAAATAAGCCGGGCACAGTGGCTCAT
GCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGTGGATCACCTGAGGTCAGGAGTTCAAGACCAGCC
TGGCCAACATGACAAAACCCTGTCTCTACAAAACAGTACAAAAATTAGCCAGGCTTGGTGGCACACATCC
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FIGURE 1, page 62 of 93

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TGTATTTTTAGTAGAGACAGGGTTTCAGCATATTGGCCAGGCTGGTCTCAAACTCCTGACCTTGTGGTCC
ACCCGTTTTGGCCTCTCAAAGTGCTGGGATTATAGGCATAAGCCACCACGCCCAGTCCATCTGAAGTTTT
AAAATGGCTGCAGGTATCTTAGTAGGAGACTAATTTTATTTTCCAATGATTAGAAAAAAATGACCAGACC
AAGAACTCTAGGGTTATGTTCATCTCATATCCTGTGCAGGATGTTCTGAGAAGTTTCTATTTGTATCTG
TGGAGTGGTTCTAGTCTTGTTCATCTTGCATTTTAAGGTTTGGAGGTATTTTATCTTGCCTTGCTTCTTT
ACCACCTTGCTTTAATTTCCCCCTATATTGCCATTTCTAAAGTAATGACTCATTTTCAAGGGTGGGTCTG
AAAGGAAAGAAATAATAAAACCAGAGATCTGGAGCAGTTTCTCGTTCATGGTCTTATTCACTTTTTAATA
AGAGCATCTAGAACAGTGAGTGGTGCCCCAGCAGATATCTGGAAATTTTTGTGGAATTGAATTGAATTTG
TTCTTAGAATAAATGACAATAAAGAAAATAGTATTATGGAAACTTTCGACCCAAGGGAAATATCAAGGCT
AAAGTTGCTATATTCTTTTTCTTCTGATGGATGCTGAGTTTTTCTCCTTAAAAAACAAATCCACATTTAA
ACATAAGGCATTGTTTGATGGCCTATCACATTCAGTAGAATGGATTTGAGAAATACGTGTAGGATGCCTA
TTAAAAACTCTGTTTTGAAATTAAACCTAAGACTATAAGATTGTCTGTTTAAAAAAATTATTGCTGCTGT
AATTTGAGCAAATCTGAACTATATTGAACTTTAGAAATTCAAATGTATGCAATCTTGTAATATAACTTAC
TCCATCGGTAGACATAGTTCTTTGTCCCACCTGGCTTCCAGCAGTTTGTCTGTCTGTCATTAGGCTAAAC
TCTTCATGTTCCTAAACATATTTCCTCAAAAGGGGACATATTTCTTGGGTCAGATGTAAACATCAAGCT
AAGGAGTTCTGCTGTGCGTCTAGACAAATAAGGTTCATTTTCATCCTCTACATAGTGTTAAACTTGAATT
TAAGATCACACAGATTCCTTTACACGTTACCAATGTAATGATATAGACAATCTCACTTTATTCATTCACT
CTGTTTAATTCATTCAATAAAAACGTATACATTGGCTGCCTACTGTGTGCCAGTTGGTGAAGATATAAAG
ATGATTAAGGCAAGGGTCTGTGCTGACATGCCTAATGGGCAGGCTGACACACCTAAACGCCAGGGAAAAA
GAGGGATGAGACCTGGGCCTCTGAAGCCCTGGCCACCTGGCTCGAAGCTCACTTTAATGTGCTTCTGGGT
GTATTCCATGACTTTTTAAAGGCGCTTATGTTTCCTTTCTGGTAAAGCATGTTTAACATGCAAAATGCTT
ATTTCATTGAGTAGCTTTTAAAAAGTGTTCATAGAATGTCTAGAACAGTGCTTGTCTAATAGAAGTATAA
TTCAGGTCACGTAGGTAATATTAAATTTTCTAGTAGCCACATTAAAAAGTAAAAAGCAACAGGCAAAGTT
AATATTTTTTTTTTCCTGAGATGGAGTCTTGCTTTGTCACCCAGGCTGGAATGCAGTGGTGTGATCTCG
GCTCACTGCAAGCTCCGCCTCCCGGGTTCAAGCCAGTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGACTA
TAGGCGCCCGCCACCACACCTGGCTAATTTTTTGTATTTTTAGTAGAGACGGGGTTTCACCGTGTTATCC
AGGATGGTCGTTAATTTTAATAATATATTCATTAATTTTAATAATATATTCATTTAGTCCTATATAAAAA
AATTAGCATTTCAACATGTAATCAATAGAATATATTATTAGTCAACTATTTTGCATTCTTTGTTTTGTAC
CATCTTTGAATTTCAATTTGTATTTTATACTTACAGTGCATCTCAATTTTAATGCTAAATGTCATCGGAG
ATATTCGATCTCTGTTTAGCTTTAATATATTTTTGGGTTGAAAAAGTAAATTCACATAACCAAGTTCTTC
CAAATATACTTGAAAGTGTTTCTGATAACTGAGTTATCAACTTAAAAATGTAAGTTAATGACAATAAATG
AAAGAAAAAATTCTGTTCCTTAGCTGCACTGACCACATTTTAGTGTTCAATAGTCGCAGGTGGCCAGTGGC
TATCATATTGGATAGTACAGCTTTAGAATGACAGTTCAGTGCAACAAGTGCTATAATAGACTCATGAACT
GGAAGCTCCGGGAAGTTAAGAATGGGATCAATGAAGTGGGTCTTGAAAAACCAATAAAAATTCACCACGT
AGAGAGGAGGAGGGCGACTACTCCAATTCAATCTTTTGAAAGCATGTGAAGGAGCAACAGTAGACTTCTT
TAATTATTTAATAGTAATTTATTGAACATGAATTATGGGAGGTGCATGGTGTGGGTGCTGGTGAGACATA
GTTCCTGAGCTCAAGTAGCTTGGTGTCTAAATATTCATGGGCCCATTTTTCAGAAAGGATGGATATGTGT
GTGATCCTGGGTGTGCCAAATGCTGTGGCTTCCTGAAGCTTAGATTTCCAGCTTGTCACCTTCAAGGTTA
CCTTGTGAATAGGACTTTTTTGAGCTGTAAGTAAATTTACTTTGCCTATTTATTTCCAATGGAAAAAAAG
CTTTTTTAAAAAATAAATCTCATCTTATTGCCTATGATTGGCCAAGACAACATGGCCCATACAGAAGGTT
TTTGATGGCTTCTGAGGTCTGTTATCATTTGCTTATTGGCATTTCAGCTGTCAACCAGGGTTCTGTCAAA
TTCCATTCCTGCCTTTAGCTCTTTTACTTGAATACCTGGGGCAATGGCAGAAGTGGTTGCTATTTGTCAC
CTTTCCAGGATGTTAGTCGTGTCCTTGAGACAAATAGAAAATTTAAAGTCAGATGACTTGATTCCTCTGC
CAGTTAAGACCCTTAGAGAGTCCTCAGCATGTTGCTTATTTTTAAATTTCAAGTCCCTGGTAAGGATCAA
GTAAACTCCCCAATTTGCAGATTTCTATCCAGTTGACTATGGATTTTGCCTGTTGCTTTGTTTCCACCAA
CTCTCCCTGAAGATGAGGCGCACAGACAGACAACTCACAGGCAAGAACAGCCTGGTCCATCTTGAAAGAT
TCTCAAGACTATTCTCCACAAGATAATTGTCTACTTTTAAAAATATTCAGTAAAGGGAATTTTTGCTGTT
ATCCTTGGTTGTGTTTTTAGTATCTCATCATCCTTCTAGTTGTAGGAGGCTTTTCCTAACATCTAACCCA
TATGTCTGTTGTCTCATCAGGTGTTTCTATTAAGGCTACTTCCCCATCAATCTTAATTTTTTTTTTAATC
TTCTGAGATGTATAGGTTAAGTTGAAATCAGAGACTTTCATAAAATGGTAAGATGGCCATTTAAATGCAA
CTATGAGGAAATAATGTAAGCAGGATTCCATTGGAGAACCAAACACTAGCAACAACTAACTTGGTAATCA
ATGTTGGGACTTGAAGTTAGGCTAAAATCAATAGTAATGGCACTCGTATGTACAAATGCAGAACTTTTTA
CACACAATGATTTTTCCCTCTGTTATTATACACTAGCTGTGTCTGAGTAGACAGTCCAGCTCCACTACCT
GCAGTCCACCCTGGGCTGTGTAATCTGAGCACTGATGGGCTGTTATTTGTACGTATTACTTCTATGACAC
TGTTTTTTCATCTGTGTTAGAAATGTCTTTCTTTCTTGAATAAGCTGCTTCAATTTCTTATAGACAGATT
CTGCTTTTATGACCCTTGTTTCTACAAAGTAATCTCTACTCATGCTGAAATCTCAGACAATTTTAACAAA
TATTTAGAGTACTTAATTTTTCTTTGAATTCTAAATATTATCCTTCTTTAGTTCACCATAGTTGGATATT
TTGAGATAACTGTGGAGGAAACAGCACTGATCCTGGGGCCATGAAACCTGATTTCAAGATCTAGTCCCTT
CTTTAATTTTGCACAACTAATTTAATCACATTCATCCTTAATTTCATCATCATTAAAATAGCAGAGAATA
ATTCCCGTTTCATGGAGTTGATATGCAATGAAATAGCATATCAATGTATGTATGAATGTCCCCCCACATA
GAGTACTACACAAATGAAACGTGTCACTCAGCATAACGTTATGTGCTCCTTCCTGCAACTGGATTGCACT
CCAGTGGGATTTCATGCTGGTGAGATGGCTGTGCTGCTGGACTTCATGGGACACCAATCTTTGAAAATAA
GCCTGATCTGGCTGGGCGTGGTGGCTTATGCCTGTAATCCCAGCACTGTGGGAGGCTGAGACGGGCGGAT
CACCTGAAGTCAGGAGTTTGAGACCAGCCTGGCCAACATGGTGAAATCCTATCTCTACTAAAAATACAAA
AAAATTAGCTGGGCATGGTGGCATGTGCCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATCAC
TTGAACCCAGGAGATGAAGACTGTAGTGAGCCGAGATTGCGCCACTGCACTCTAGCTGGGGCAACAGAGT
GAGACTCTGTCTCAAAAAAAAAAAAAAAAAAAAATAGCCTCTAACAAAAAAAAAAAAGAAAAAGAAAATAA
ACCTGATCTATAGATGAGGCCAGTGGATCTTGTGAAGAGTTGAAAGGTCAGGTATCAGTCTTATACCATG

FIGURE 1, page 69 of 93

TCGGATGGGGCAATCGTCATAACTTTTTAAAAAATTATTTATTTATTTTGAGACAGTGTCTCACGCTGTC
CCCCAGGCTGGAGTGCAGTGGCATGTTTTCGGCTCACTGCAACCTCCGCCTCCTGCGTTCAAGCGATTCT
CATGCCTCGGCCTCCCTAGTAACTGGATTACAGGTGTGTGCCACCATCCCTGGCTAATTTTTTGTATTTT
TAGTATAGACAGGGTTTCACCATGTTGGCCCAGGCTGGTCTCGAACTCCTGACCTCAGGTGATCCACCTG
CCTCAGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACCGTGCCTGCCCCAATTGTTACAGCTTTTT
AAGTGGATTATATGCCTGCTTCAGGCATTAGACATAATAAGTTAATCTGTTGATAAGTTTCTTCATTTCT
TAATTTTCAGTTGTGTTTTGATGTGTGTGGTCTGGGTGAGCGGCTCAGTGCTGCTGCTGTGGAGAAGGCA
TGATATGGAAGGGATGTGACTGTCCTTCTTCATCTTCATAACGGGGCCAGGACTGGGGTGAGGTGTGTGA
GATGAATGAAGCACTGGTTTTGATACAAAATTTAAGAAAAATCAAATTCAAGAGGTAATATTTTAATACG
ATATTTGTAAAAAATCAAAATTAGTGCAAAAATTTGTGATGAGCAAAATGTTAGATAAAGGCATTGTTGC
TTTTCTTTTTCTGTGTATTGTAACACACCATCACTTAGTGGAGAAACAGCTCTCACTTTCCTCCTCCCCA
GATACAACCATTTATGTTGAATTAAACTTCTAGTTCTCCTATACCTGTGAGCATCCCCCAGGCCCCTTGG
TATGGAGAAAGCAGTTTATTTGTCTTAGTAAGATTATAAAAGTGGCAATAAAATGTGAATGTAATGAACA
AAATGCACATTTTGTGGACCAACTCGTTGTTTTAGATCTATTTTTGAAAACTCATTAGGTATGTGCATGA
GGCAAAATAATTCAAGTGCAGTTGGATATTAAATGAAAAAGTGTCAGGTCCCCTTTTCTGCCATATTCTC
TTCTGTGTCTTCATTAGTGGAAACCATTTTGACCAGTTCTTATAATTCTAATGATTTGCTGATGGCTCTA
ATTCTTGGTTTATCAACTTCAAGCAGAATGTCTTGACATCTTGGTATGAAAGTTAAAGAATATGAATCAT
TTGTTCTCTCCCTTCTCCTTTCCTCTTTCTCTGCCTCTCAGTTTTTGTTGTATGCTCACGGAGTATGTGT
GTGAGCATGTGTGTGTGTGTGTGTGCACGCGAGCACGTGTGTGTGTGTGCGCGCCCATGGGTCCATTTTT
GCATGGCAGGCTTTGTTTTAGAAAGATTGGTTACAACAGCTGCCCCACCAATCTCCTCTACAGGGAAGGA
TTCCTACTCTGAGACCTTGGTCTTTTCCAGGCAGATCACTTACATTTCCTCACAGATTATTTCTCATCCT
GCAGCCTGGGTCCAAATGGGCTTTGCTGTGAACAGTGACTCTCAGGCTTCTGGTCTCTGCTGTGCTTGAG
TGTCGTTGAGATGCTCCATCTCCTCCTACTGCACCCACCCAGCAATCATCTCTCTTTCAGGAATTCACCA
AAGTCTTTTTTAAAATTATTCTTTTGTTTTGAGACAGAGTCTTGCTCTGTTGCCCAGGCTGGAGTACAGT
GGCGCAATCTCCGCTCGCTGCAACCTCTGCCTCCTGGGTTCAAGTGATTCTCCTGCCTCAGCCTCCTGAC
TGGCAGGGACTACAGGCATGTGTCACCACACCCAGCTAATTTTTGTATTTTTAGTAGAGATGGTGTTTCA
CCATATTGGCCAGGCTGGTCTCAAACTCCTGACCTCAGGTGATCTGCCGGGGTCCATTTTACGTGGCAGA
CTTTATTTTAGAAAGATAGGTTACGACAGTTGCTCCACCCATCCCCCCTGCAGGGAAGGAGTCCTACTCT
GAGACCTTGGTCTTTTCCAGGCAGATCACTTACCTTTCCTCACAGATTATTTCTCATCCTGCAGCCTGGG
TCCAAAGTGCTGGGATTACAAGCGTAAGCCACCACATCCGGCTCACCAAAGTCTTTGGGTGGTTGATGTC
ATATGCCTCCAGTTGATAGCACTTTTAAGAATTTTTCCTTTTTGTATGCTGTTATTATTTTTAGAAGGCT
TTTGGATTATTATTGTTAAAGAGTATGCCATGTCTATCTTTTAACTTTTAAGCATCTATTGCTTTGTTAC
TTGTACTTTATATATATGTATATCCTTCCCCCAATAAGACAAAGAGTGCAAATAATCACCTCCCTTGCCT
GTTGTTTGGGTTTAATTCAGGAGTCAGTGGAATTAAAAGCCTAAACTCAGTATAGTTTTAAAGCAGCAGT
CCCCAACCCTTTTGGCACCAGGGACTGGCTTTGTGGAAGACAGTTTTTCCATGGACCAGTGTGGGGGCTG
GAAGGTGATTCCAGGATGATTCAGGTACATTACATTAATTGTGCACTTTATTTCTATTATTATTACATTG
CAATACATAAGGAAGTAATTATACAACTTACCATAACATAGAATCAATGGGAGCCTTGAGCTTCTTTTCC
TGCAACTAGACGGTCCCATCTGGGGGTGATGGGAGACAGTGACAGATTATCAGGCATTAGATTATCATAA
GGAGTGCACAACCTAGATCCCTTGTGTGCACAGTTCACAGTAGGATTCGTGCTCCTATGAGAATCTAATG
CTGCCACTGATCTGACAGGAGGTGGAGCTCAGGCAGTAATGCGAGCAATGGGAGTGGCTGTAAATACAGA
TGAAGCTTCACTTGCACGTTCACTGCTCACCTCCTGTTGGGCGGCCCAGTTCCTAACCAGGGTTGGGGAC
CCCTGCTTTAAAGAATATGTTTGTGGATTCATAGAGGGAAACAACACACACTGGGGCCTTTCGGAGGGTG
GAGGGTGGGAGGAGGCAGATGATCAGAAAAAATATTAATAACTAATGTGTACTAGGCTTAATATCTGGGT
GTTGAAATAATCTATACAACAAACCCCCATGACACAAGTTTACCTATGTGAGAAACCTGCACGTGTACTC
CAGAGCTTAAAATAAATGTTAAAAAATTCCCTCCAAAAAGGATATATTTGCATCGGAGTTATATTTGTAT
ATGAGTATATATTTGTATATATAAATATACTTGTATATGAAAAAAATATCTTTTTTCTTTCATTTTATTT
TCCAAACATTAAAGTCGGGCACATTGGTTAGGAATTTCACCAATACTTTTTACAAAACTGAGGACTTGGA
TGATAAAGGCACTTTTTAAAAGATTACACACTGGCATGGGGAATAATACCTTTATAAAGATGATCTATGT
GTTCCTGAATATCCCGATGCATCTCCTAGCTGGATCTTCCGCTCCACAAAAAATTCATAAGATGAGATTCT
TGAATTAGAATGCATGCCTTAATGTATTAAGTCTATGTAGAGAGAGTTATTTAGTCCATGTAAATTAAGT
GGGAATATTTTTATTTGATTACTGTTTTATCTGGATCTTGCCCACTTAAGGCCTTCAAAAATGAAATTTA
AGGCCTGTTAAGCAGACCCAACATCAACAGCATATTCTCTCTCTTGTAAGTATTGTCTAGTTGATAAA
AAATTTCAAAAACATGTCTTAATCAAAAACAAGATGATCCAGCACAGGTTTAATAAATGTTTTGTGAATA
TGGCACATTCGTGTCTCATTACTACAGTTTTCCTATGCTGTCTTTCTCAATAATTCCCCCCAAAATTGTA
GTGTTTACATTATGGCATTTATAGTTACCTCTGAACCTAAAAAATTAACTTCAAAAGTATTTAAAAAAAT
CATTATATTTAAAACCATTTCATGTTTAAATGGTTTGTACAGGGCAATGAAAGGAAATGTAGTAATAAAC
ACAGAATCAGATTTGGTCACTAATATTTTTCTGCAGTTGAAATATATGTAGACTGGCTTAGGGTCTAAAT
AGCATTGAATCCTGTTACCTTCCATCTATAATCAATTAATGTATTATGACATTGTTGTCCTCAGATCACT
GGGATCTCATGGTAAGTAAGTAAAGGGATTATTCTGTGCATTTTCCCAATATCTATATTAGTTTTAATAT
ACCTTTATGTTAATGTATGACACTGACACTTAGTAATTGGATTAACTTCCTATCAGAATTTGTTTTTCAC
TCATACTTTGTATACATGTCTTAAGGGTAGGGTAGATGTACATTTTTTTCTGTGTTAGCCTATCTGTTTC
TGTGACACTACATGCTTTCTGTCCTCCAATTTGTGTTTCTTTCCGTGTACAAATATGCATCATCTACCAT
CTACATCTACAAAACATGTAGGCTTCCAATGTTTTCATGTAAATACATTTCATGAGTCCTCAGTAGAGTG
TTAGATGAGTGGTTAATTAGTAATGTTAATAAATGTAAATTACAATAAAAACATTTATAATGTTAATAAA
TATAAGTTTATTGAACTTAAATAATTTAAACATCTTCTGAAATGTAGTAGAAATTATGATTAGCCATAAC
TAGTACAGTATTTTTTGCTTGTTTAATTTTTTTGGTGATATTCCATTTGTGGAATGAGTGTGTGTGTGTG
TGTGCAGTACAGACAGAAAGGAGAGAAACATATCTGCATGTTATGTTAGAAAGAGTAGTGTTAGCTACCC
TACCAAATTTACATACTGGCTGAACACAGTATGTAAAAAATTATTTTTTTAGTCCATTGCTGGTGTTCCT
TGTTGTTGGGTGACTCTATTCCACATGGTGATGCAGGGAACCAATCTCCTTCCTTCTGTGGCTGTGTAAT
CCCTTGCAACCTTGAAGTCCTCTGCATCTAACTTTAGGATGAGGAAAGTGAAGGTGGAGGATATAGCCCT
CTTGACTGCCTTGACCTGGACCTGGAACATCTCTTTTGCTCCCATTCCATGGGGAAGAACTAGTGACATG
GTGGCCCATAGCTGCAGAGGGGAGGCTGAGAAATGCAGCCTCTGGATAAGAAGCCTACTCCCAGTGGTTA

FIGURE 1, page 70 of 93

CTGTACATTGTGGGAGGGAAGCTTGAATTCTGATGGACAGTGAGAACCATTCTCCACACAATAACGAAAT
GACGTCTTCTCAACCTTGGCAATGTAGCATCCTGTGACTTAAGTATGTAAATAATTATCAGTACAGGTCA
GTGAAAAATTAGGTCACCTTTCCCTTCCACTTTTAATTCTATAGTTTAATTTGCCTATCTGCTACATATT
ATATATATGGGAATAGATAAGATTATCTATAAACATGTATAAATTTGTTTCCTACACTAAAAAGAAAAAT
GACAAAGAAGAATTAAGTTAGTTGCCCAAATCCACACAATACCACCAGGAGAAAGTCTAGGAACCATACC
TTCTAAATCCAGGTCTACACTTCTTTAGTGCACTAAATTTTTTCCTAATATAGCTCTGAGGAGACTGGTG
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GATGTATAACTCCTGATTTTCTGTGATGACAGAGAAAATACTGACCTGATTTGGGTAACTCTGAGGTTTG
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TATTCTGTAGAATTTGGTTTCGCATTTTATTTTTATTTTCTTAGACACTGGTAGTTGGAAATTCAGGAAG
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GATTAGGAACAAAACGATGGCAGAGAAATGAGAGTTTAGAGAAAGGAGAGATAATCCTGAGTTACCTTAG
GAAGAGAAAATTTCACAGAGAAAACGGCCCCCACACTGATTTGGGGAAGATGATTCAGACTTGTCTCAAT
GGCATGAGGAGCAGGGGCCAGATGGGAAAGGACATCGTGGTGGAAATGACACGATGAGCAGAAGCTTAGA
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CCCACACAAACCCTGAGCTTTCTTCCCCTCCAGGCTGCTCCATCAGTCAGACAGGAGTGCCTTCTCAGGG
GATCCTCTTCCTCATCTTATCGGGCCACTCATCTCGTCGCAGACATTCCCATACTCCTGGTTGACTTGCT
CTTCCCTCTTTTTAACTGACATGAGCAGGCATCACCTCTTCCAGGAAACTTCCCTGACACCAGGCTGAGT
CTCTCTGGTGTCGGGGAAGGCTTCTGTATTACTGCATCTGCCATTTTGATTTAAGGTTTTCTGCTCATTC
CAACTCAACAGTGAGCTCTTTGAGGGCAGAAATTGTGTCTTATTCATTTTTCTTGTTATGCCCTAAAAAT
GTATTGTGATAATATATAAGTAACGTACAATTTACCATTTTCACCTCTTGAAGTGTATAGCTCAGTGGCG
TTAAGTGCATTCACACTGTTGTGCAACCATTATCACCATTCATCTCCAGAACTTTCTCATCATCCCAGGC
AAACTCTGTATCCATTACACAATAGCTCTCCATTTCCTCCTGCCCTCAGCCTCAGGAAACCTCCCATCTA
CTTTCTCTTTCTACGCGTTTAACTACTCATATAGATGGAATCATCCAACATTTTTCCTTTTGTGCCTGGC
TTATTTCACTTGACATAATGTTTCAAGGTTCTTTTATGTTTTCTTATGCGTTTTTATATCTCTCTATCT
TTGATAGCACCCAATACATAGAAGACAATGAATGTTTTTGTGAGTGAAAACATAAGACCAGAAAGAAATA
GGATGTCATATTCTAGGGACACTCAAGACACTTTCTTGAGGACAGAGGCACTGTAGCTTGGAATTTGGAA
GATGAGGTTGGCAAGGTGGGTGGGGAAAGGATGGAAAAGTGATACGTTTCTTGAAGCATGTGGATTTGCT
TCCATAAGCAGTGGTGGACCAGTGGGCACCCTTATCTATTAAAAGAATGATTTTTTTTGTGACTCGTGTA
GAGCACTGTCTTAGTTACCTACCCCAGTGGTAGATAAGAGAAGCGGATTAAAAAGAGATCTGAACCTGAG
GAAATGGAGACTACCAAGTTTTTTGTAAATATGTCTGTTATAACATATATTATCTAGTACTTGCGATGCC
TGTGCCAAAGCATGCTTTTTGGTTTAGTTAAGCCTACTTAGCTCGCTAATTTCAGTAATTTTGGCTTGAA
TTGCAAAAAAGTTGATGGGGGAGATGGGGGAGTCTCTGACATCCTTCCCCCACTCACAGGTTTGAAAAATA
AAATTATGAAGAGCAAAAGGATCTTTTTCTGTGGTAAATTGTACTTCATGACAATAAACGAGTTGTGGTT
TTAGTGGTTAATTTATAAATTAGGCCATCTGGTTCTTCTGTAATCTAAAGATTTTTATATATATGTAAAA
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ACCATATTCAGCTGCCAAAGTGCTGCTGACATACTGTCCAATGAGACACCCAACGCCTTTGCATTACAGC
CAGCAAGGTGTGGAGCTAGATGTATTGATCTATTTAATAATATTAGCTTCTCTTCTCTGGGTCGGACTTG
GCCCAGAGCAAGTGAACAGGACCTATCTATCTCCTTCTCAAAAGTCACAGCTTTCTTACCAAATTGTACA
ACTCAAGCCACAAAGAAAACAAGTCAAGGAAAGGACCAGAGGAGCACGAGGGCACATGCCTTGTTCCCAG
ACCCTGGGACCAGCTCCAGCTCTGGCTCCTTGCAGATCCCGCTCTTCTCAAGTTCTCTGGCTTTGATCCT
AGTTTTCTGCCCTACTATTCCTGACATGTACAGCACTTAGCAATTCATAACTTGCTTTATTAACCAATAT
CTCAACAGAACTTTTAAACAACCTGGGAGGAAGCAGAGTGGGTGTTACTGTCCTCATTGCACAGATAATG
AAACTGAGGTTCAGAAAGGTTGAGTGTCTTGCCCAAGGCCACACGGCTTCTTAGTGGAGAAGCCAGGATC
TGCACCAATGTCTTCCATTGGACACACTGCCACTTAATATGGTACTTAGTTTTTCTTTCTAGATGAAGCA
GTATGAGGAATTCTACCATGGATATCTCTCTCTATTTTTTTAAACTGCAAAATAATGATAATGATAATAA
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GGTAAATAAGTTGCCCAAGGTCACAGAGGCAGCCAGATTAGTGACAAAAGTTTGAGAGTACTCAGTTTGA
ATTTTACATGTTCCGTGGATATGGTTTATGCCAAATACCTTCTCCTTTCTAGACCTCAGTTTCCTCATGT
ATCAAACAAGTGGACTGCACTATACAACTCTGAGGTCCCTTCTAGCCTGAAGATTAGAGTCTTTTATGCC
CACATGATATGGAAAACATTAATGCTGGCTCTTTAAGACTGGAACCTTGTCATTTAAAAAAATAAGCTCT
ACTAAATTTGCAGTAAACTGTCCAAATACGATCTCTGGTCTCTGATTTGTATCTCTCACAGAGCATGATA
CAATGCTAGACACATATATACTCATTAAAAACTTGCTGAATTAAATTGTAAAACATTCCTCCAGATAGAC
CGTAAGGGTGAGCTGATGCCCTAATATGCTCCTCAGCTGCTGACTTAGGACCCGTGGGTGACAAACCCTG
TCCTTGTTGTTCCATCTGTGACAGTGGGCAGTGTCCAAAATGAGTCTCTTCATCAAAAGTGAGTCCAGGA
AACTGGATCAGAGTAAGTAAGGAGTCTTCCTTGCTTCTTTTTCTCTAAAATACAATACAGTGCATTCTAG
CAAACTACCAGCATGCCTATAAATCTCATTTTAAAAATATCAGGAAATAGATGCTCATTGATAAAGAGGG
TAAGAATGAGCAAGGGAGAGAGTCAAGCCTGTACATTTGTGCTTAGGGTATTTTCATTTGAGAAATTATC
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TAAATAATGTCATTTTCCCAGATACAAAGGGGAAACCATAATGCCTTTCATATGCCTTCTCATATCTTCA
GTGTTTCTCAAACCCAGCTGTGGGGTCTTTTTAGGGAAGATACAAGGAGGGTGAGACCATGTGGAGCACA
CACTCAGCAGCCACTGTGAAGTCATGGGTCCCTTGCTACCTTTGGAAGCTGACAATCTGCATGAAAAGCA
GCCCCTAGGAACATGGGTAGTGGCCCGGGATCCAAAACTCCTGAATCCATAAAAGGGCTTTTGACTTCTT
GTTCCAGGACAAGTGACATCTGACATGCTTGCCTGCTTGTTTGCCTTTCTTCCTTCTCCTATCCGTCTTT
CCATCCATCTGTCCATCAGTCTATCTGTCCATCCAGTCATCCATCCATCCTTCCATCCATTCGTCTATTC
ATCCATCCGTCCTTCCATCCATCCATCCAAGATTTATTGAGCACTTACATGACAGGAAGTATGAGACACA
AAAGAAAATTCTACACAATTCTCCTAGGGACATGAACTAATGGTTAGCAAAAATATATGGGAAGTCCTGC
TTCAAGTAAAATTATGACTTAAGATATACATCAGATATTTGAAAAAGATATTTTTAAGTTCAACATTGAA
ATTCTAACTACATTGTGTCCTTAATTTCTATTTTCTAGTTAGACTTTTTTGAAGATACAAATCATTTGAA
TTATCATTATTATTGTTACTTGATTTATTTATTCCACATGAATGGTAAGAATTTTAAAGGAAGGTGGGT

GCCCTAAAAAATACATTTATGCCAACTGGATTGAATCACCTTGAATCACAATGAGTACAACAACTGCTAAT
GAGCTAACACTTAATGAGTAATGACCAGGCACCAGACACTGTTCTAGCACTTTATACTTACTGATTTCTT
TACTCTTCATGATAACCCTATGAGGAAAGTGCTTTTTTGTTAAGCTCCATTTTCAGCTGAAGAAGCTGAG
GCCTGGAGAAGTTACATAGCTTTCTCATGGTGTCTCCACTATGAAGTAGCTGAGCTGAGATCTCACCCAA
GGCCCTGCTGGGTTCAGGCCACACTCTTAAGTACTCACAGCTGCATCACACTGAATATCATCTCCCTGCA
CTGCCATTTCATTTGAGCAGGGCTTTGCCTGTCAAGAACATTCATATCTTTTGATAAACAGTGCATTTTT
TCCCTGATAGTCTGTATGGGACAGCCTCCTTGTTTGCATCTGAAGGACAGGGACTTCAGGACCTCCTGCT
GTGGTCACCAAGGAATCACATTCAAACTTCTCAGCAAGGTGTTATGGTCCTTCTCAGTTTGCCTACGATC
CATTGAGGCAAAGGTTTCCTTCTCTCAATACACCCTCTGCTTTAGCCAGGGGGACCTCCCACTGTCCTCT
CTATGTGTTCTATTTGTTCCTGACTGTTAGTACCCGCTTGTGTGGTTTCCATGATCCTTCTTCTGCCTGG
AATGAGGCTCCTCTTGAGTCCTGAGAGCTTCATTTCTGTCTGTCTTTTGGGCTGTGCCAAAGCCCCTCTG
CCTTCGTGGACTCCCCACTGATTCATTACCAATTTTCCTCTCCTCTGGGCTCTTCTTAGATTGCAAATGG
TGCCTCTGGATTGGGTACCAAGACTTGCAGTGCCTTATTTTGATACCACTAATATGAGACCATGTTATAT
GCCTCTTGAGATATCATTCCCTTTCTAGCAATAGACAGTGATAAGCATGCGTATAGAGGGTAAACGTAGG
ACTTTGAGGTTCATCCATCTCAATAGACAAAAGTAAAAGTATGCTAATTTCAATCCTTCACACAGTAAAT
TGAATGTAATAGGTCTTCAGTAACTATTTGAGGAATGAAATTGTTATTGATATATTGATTTAACTGAGCA
AATCCATAAGTGCCACGCTTGGAGTAAAGTACAGGGAATCTCATTTTTTGGGTAATTTCAAACAAGTAGG
AGACCATCCACTATCTATTAAGGACAAAGGAGATTTGAGTGACAAACATGTTCCAGACCATCCAATGGTG
TTATTCTACTACTTCATCCCAGCTAGTAAAATGGGGCAATAAGAACCAAAAAGCAGGTACTGTCCCTATG
TAAGTAGACTTCCTAGTCCTGGCCAAAACAAAAACAAAAAAAAAACAAAGCAACACAAAACAAAAACAAT
GTGTGAAGAGCATCTTACCGTTCATTGCTTTGGATGATTTGTGCAAATCTAGTTAATGGGGGTGGATCTG
ATCAGTCTTTGTAGGAAGTCAGTATTGGCATATGTCTGGCTTCTGAATTTTCTAAAAATATAATTATTTA
TTTTTAAATCCATTCAATCAACACTGAATTTACTAATCAACTACTAAATAAGTAAAAGATCCTATAGTAG
ATCCTTCAAGAAATGGAAATTGAGACATTAGGTCACTATAAACCCCAACCCTTGTAATCTTTTTGTGGCA
ACCTTAGGAAACTTGGAATGCTTTTACACTCTGATAAAGGTTTAATTGTAATCATAGCCCCAGTGTTGC
AAAATGAGTCAGAAGATACAAAGTATCTCATAGGATAATATTATAGCTGTAGGTACTTCAAATGGACAAG
TATAACACATTATGACTGCTAATATGGATGCATTGGGAGGAAAATAAGCCCTAAGAAGCAATATGCAGAA
AAGCTATGATTGCTGGAGACAGATAGATCCAAGAACCTAGGTAATTTTCAGCAAACTGTGGTTCCACTT
TCGCCTCTTTCTTGACATTGACTGTGTTTTTAACAGGGAAAAAGTTATCTGAAATTTTTGATAGAGTTCA
AACTTTAAATCGTGTTCACTTTGCTAAAACTCCACTGGATGGAGTGGCAGAAGAGAAAAAACACAGAAAT
AAAAGAAAAGCAGTAATGGAGAATGGAAAATCTTTAAAGATGCTACCATCCTGAAAAGATTCGAAAGCAA
GCCCAGGAAAGCCACGGGGAGGGAAAGAGCGCTTAGAGGTGTCCCCAAAGCTTTCAGAAGTGATGAGGGA
AACCCCAGCTCTTCTTGTTACTTCTTGGCATTTTGTTCCTCTATACGTTAGCTTTTGGTTAATCTTTCAT
GTTACTTATTATCTCTGTTTTAAAATTTCACATTAACTCATTGGTTTCATATCCCACTTAACAAATTAGA
TATTTTCCTTGGGCTTATTAAGAAAATTATTTGCTCTCATATGTTATGGCTTTAGATTTTCTGTGTAGCT
AGGACTGTTCTTAAATTTTTATCTTTACCTTTGTTATTTCTCTGAAGCATCCCCATTGGGGTGGCAGTGG
GGGGTATTAAATGGTTATGTAAAATTTACATGTAATTGTGCAATTTACACATAGCCTCAAATATAATGAG
GCCTAGTCTAGCTGCCCATACCAAGAGGATATTATAGTTGCCAATAAAATCAGTATTATTTCTTTTTTTT
TTCTGTTCTTTTTTAGCTTCTTGCAAACATTCACTCAGAATCCTTTTTGAATATCAGTTTTGTGAAAAGC
ACCGTGCTGGGTTCTTTGGGAAAAGCCAAGATGAGGGCAAATGCATCCTCCTTCCTAGTGAGTCTAGCAC
ACAGATGACTCAGGAAGTCATGCACTGGAGGAGGAGTATCTTCTAGAACTGGGGAAAGGTTAAGGAAGGG
ATCAGAAACCTTTTTCACTCAACCAATTACATTTTCCTGAAAGCATGTTATTAATCGTACATGATCTTGC
AGACCCCAGATAGAGACTATATCACTATATCAATTGTTTTCTTGAACAACTGGAGTTAATTCTCATATGT
TTGGTTACCCTTCAAGTATTTATGTTTAGGATCTGTTTTCTTCCTCTTAACTTACATTCCAAAGTTTAGG
TATCCTTCCCCTCCATTTGCTGTCCAAAACAGCATCCTTTCATGTAGCTACATGCCATTGGAATGATTTG
GTTTTTGCCATGGATTCCTAGTCCTAAATTTGGACTTTTATTGGTATCTAAGATGTCATGGACAGAACCC
ACAGATGTTGTACAAAAAGGGCTGAGTGGACAGTCCAACAGAGTTACATCATCTGTTCCAAACACCCTTG
TAATGGTTGTATCAGCGTCAATGTCTGAGTTGCTGTCCTGGTTCTCCTGGCCAGTCCTCAGCTGGCCATG
CCTGTTCAGGCACCAGAGAAAGCTTCATACCTCAGGCAAATCTTTACAAGGGATTTGAAAGGCAAGAAAC
ATGTATTTTGGAGGTTTTACCTGTTTATTTCATGTATAGCTTCATATTAACAGATTTTGCTATCACTTAA
AAGTAAATAAAATGATTTTGATTTCTCAAAATCATCTTATAATTTATTAATCTATTTTAAGGCTTGCATT
TACATTTAATCTTCAAATCTTGATGCATTTTCACAGAGTTTCTTTAGTTAGTTAAGGATATTAATGACTT
CCTTTAATAGTTGATGAAGTGAGTCATCATCGACAGTGAGTCACTAAGGCCAACTCTTGTACCTGCTCTT
AAATAGCAGTTGTTTTACTAGATTTGTACTGAAACCTTTTTAAAAATCTGTTTGTCTTATATATATAACAAG
CATTTCCAGTAGTTAATAATACTTTCTTAGCTCTTCAATCATTTTATGAGAGCATTACAAGAAAAGCAGG
AGATGGGGAAAGAGATATCTTGTTTGCCATGTAGGATGCATGAAATTCTTACTTAGTCTGTTGTGTTTTG
GATTCGAGAGAAAATATGTAATGAATCAAAATGTTTCCTACAGTCCTCTGAAAAGATGTAATGAGACAGT
CTTCCAGCAGCCTTTGATCATCTGGGAAGTCATTGACTTTGATCCTTATCCTATCAGGGGCTCTTACCCT
GGGGTCCATAAATACCCAGGCATTTTTAAGAAGTGGATTTCAGTATAACTTGTTTCATTTTGTGATTTTT
AAAAATATTTTGTTTTATGCACTTAAAACCTTAATCTGAGAAGTCATCTGTAGACTATACCAGATTTCCA
AATGGAATAAAAATATTTAAGAACTCTCTTATGTGTGTGTTTCAACCTATAAATTTTATATGTGTAGCTC
ATGGTTAGGTGGTAAGTAGAGAATTTGCTATCTGTGTAATATTTGGTACTTTTTATAATGAAAAAGGAAG
TAATACAATGATAGGTACCATTTATTTGTTGACCACCCATATTTCCAGGGAATGTGATAGATACTTTTT
ATATATTCTTTCTAGTTTTCACCATAACATGCTGCAGGGATAGTGTTACCATTCTCATTTTGCAGATGAA
GAAATTGAAACCCAGAACAATTCGTTCATTCATTCAAAAAATATCCATAGAGCATACACTAAGAGAAGGC
ACTCTGCTAGGCACCAGAAATTGAATAATTGACCCCAAATCACCTAACTCATAAGTGGCAAAGCTGGACC
TAACAAAGCCCATTATCCCTTCTATCACACATTCCATCCTCATAATATCATATTCTACATAGAAAAACTT
AACAGTCCTGTTGAGACACTTGGAACTCTAAGAAGGTAGTCAACAGATACTTTTCTCTTTATATAAATAT
GATATCTAATTAGCTTTTCCTGGAAAGGAGTGATTCTGCCTTTTTTTAATTCTAGCATTCCCTGAGCAAA
TTAGAGCCCAGGTAATGATTTCCTGAGATAAGTCAATTCTCTTCTAGGACAATCTCTAGTCTTGTCATCA
TGAGATGGAATAACAACGGTCTATGTCATTTCAGTGACGGCACCTGCATGTCCTTGTATCTAAGAAAAGA
CACCTCCTTCTCTGCCTTGCTAAATATTTGTAAACTTTGCTTTAATTGGTATATGTGCCACTGTTTTGTA

FIGURE 1, page 72 of 93

TGTGGGAGGGGTTTATGGTTTTGTTTTGTTTTTTGGTCTTTTTTAGTAACCCCAATCCAAACTATTCTCA
TTTGTAACCTAAAATACTTAGAACAAGAGGCTTTGCAATCTTGAAGACCGAATACATTTTTACTACTAAA
TGTAAGGCAGATTTGAGCCACCCATTTTGTAGTGCTTGATTATGGCAACCCGAGGAAACTAATACGGTTA
CTCTTTATCTTTATTAGGAAATACTGCTGTAGTTCCTGTTGTAATCCTTAGGGAGCCAACATTGTTGATG
AGACCTAGTACCAAGCCAGAGGCCATGTTGAACTAGCAAGATATGGGATAGTTTTTACTTTCAAAGTAAT
TAGCATCTAGAGTCTAGAGAGTTTCTCTTACAGGGTGGCCTGGTGTCTTAGTCTATTTTCTGTTCCTATA
ATAGAATACCTGAGACTGGGTAATGTACAAATTATAAAGATTTGTTTGACTCACAATCCTAGAGGCTGGG
AGGTTCAAGATCAGACAGCCACATCTGGCCATCCTTTAATGAGGGCCTCATGCTGTGTCATAACACAGCA
GAGAATTGGAAGGAGAAATGGGCACATGCAAAGAGAAAGAAAGGGGACGAAAGGGGCTAACTCACTTTGT
AACTATGAGACTAATCCATTCCCTGGAGAACTAATTTATTCTCATGAGAAAGACATGAATACATCTTAAC
ATCCTAATCACTTCTTAAAGGCCTCAACTCTGTACACTGCTACATTGTAACAGGCAATTAAATTTCAGCA
TGAGTTTTGGTGGGGACAAACTACATCCCAACTGTAGTACCTAGCTACCCACTTTATTTTAGAGTGGCT
ATTTAATGACCTGGCAAGATCTACTGTGCTTGTAAAAGAATCCACCATGGGTTAAAGAAAAAATAGTTTCT
GGCTTCCAGTCTCCTTTTGGCCTCTCTCTAGAATGGCATATACAAGTTCAGTGGTTACTGACTTCAAAGG
TGGGGTGGAAGACACTGAAATGAATTTTTCTCCTTTCTTTGGTTGGTTGCTCTCTCTCTTTGTTGCTGAA
ATTTGTGTAGGATAATGGAATGAATATGGGAGATAGGGAACTATAGAAAGACTGGAGGGAAGGGAGAAGT
CTTTTCTGAATTAACCCCCCATGTGCTTGTGAGACCCTTGGACCCCAAAGGGCTCCTGACTGGCTGGGCC
CACTCCTTCTGTATATGGAGCCATAGGGCTTTTCTCTGGCTTCCCAGTTGAAGCATTGTCATATGCTTTG
ATGCTCAGCATTTCTGGCAATTTTACCTTGTAAAACTCCCGTTTCGACATTCTGAACTTAAGTAGAAAAT
GGGAATATAAGCCTCTTGTTTTTTGCTCTTAATCCATTCCAGAACTATAAGTCCCTGGGTTCTTGGCAAC
AACAGGTGTTCCTCTAGATTTTAAATCAAGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGGAAT
ATCTCACTAAAACGACAGTGTTGTCATCAATTTTGGCTTCATGGAGGGTCTTGAGCTGGGTGGAGATGGG
AGGAAGCTATCCTTGTCCATGCGGTTTGGAGACTTGCTCTAAAAAAGAGACCGTCTACTTCCCTCGTAGT
TTTTGTTTTGAAGACATTTGTAGTGTTTACCAGGAGCATACAGTTATCTGGAAAATGCAGACTGATGACA
ATAGTATTTGAAATGCTCGTAGATCTGCTTCTAGGTTGATGGAAAGAATGTATGTTCCAAGGTACAAGTG
CTTGTTGACTTTTCGGATGCAGCCAGTCTGTGCTCTTTGTCAGGTAACTCGGAATCACTCCACAGTAGCT
GTCCTTCCTGTCCATTTGACAAGCACTTAAAAGGGCAGTCTTAAGTACTTTACTTCATAGTTTATTAATT
TTTTCCCTTCTTTAGTTTGCAATCTACTCTCAGAAACTGAAAAATAATTTCTTTTACCTTTTTCCCCTTT
CTCATTTAAGCTGAAATTGATTTCTTTCTGAGCGTGTAAGGAAAAAAATAAAAAGAAGCTGTGGTTAATA
CAATTGCCTTTGCTGAACAAAAATAAAAGACTAGTTTACCTTCAAGCTGTGCTGTATCAGAGTAAGGATC
TGTTCTGTCACTCCCAGGAGATTTTGATAAGAGAGAGTACAAAATTTCATAATATCTACATAGCATAATT
GTAGCAAATATAAGAAGTATTATAATTGTTTATTTGGGGATGAGGGTGGGGATGGGTTTTTTTGTGTGTG
TTTGGAAAATTGGGAAGCTAGAAGATACTCTTAAATCCATCAGCTTCTTCAGAACTCTTCTCAAATGCTT
ATTGTCATGACAACCATCTCTTCATAAACCAAGGCTCTGAGTGTAATACAGATGGGGCTGGTAACAAGGT
AGGATTGCCATCTGCTTTGTTTTCTCTAAGGGACATTATTTTTTTGTGATCCCCAAGTCTCATCCTCAAA
TCTGAAAGTCTTGACTTATTTTTCTTTCTGGAGTCAGATAGAGCTGTGAGATTAATTCTTTTCTCCTGAC
AAACTACTTCCTCACCTGTCATCAAACAACTTACTTGTTAAATGGAGGGAAAAAAGGGTAATTATGTGTG
TGTGTGTGTGTGTGTGTGTGTGTGTGTGAAAACAAATATACATATTTTAATGATTTATTTATCTGTCTACTT
TGCAAAGTCTCCTATGAGGTACCTAGTAATTCAATAATACAGTCAAGTGTGAGATCCAGAAACAAGTAGG
AGTGAGGCAATCATTTTCCCATGAAACAAGTAAAATTATTACTGCTTTTGAACATTTTAACACCTGTGCT
TCCTGATGGTGGGGCTGCATGAAGTTTGTAAGTAGTGTCATCATTCTCTTATTAGGTAACAAATAGGAGC
ATAATTATTTAGGAGAGGAAAACCTTTTCTTGTTACCAAATTTGGTGAGAAATTTGCCAAAGAAATGAAT
GCTTACAGGAGGGATACAGCTTAATATCTTCATACTCCCCTTTGTCAAAGATACAAATGACATTTTCTCA
TATCAACTTCCTACAAAAAGTGAGGCCATACATTTTTAAAAAGAATATACCCAGTATTTTAAAAGTTTGT
ATATATCGTGATCAGAATTAAGATATATCCAGCTTTTGAAAAAATATACATATTTAGCCATTAAAAGGTA
TGTGGTAAACTAAACTGATGAATAAAGGTTATGGGAAATATTTCATAAAATTTATATTTAAAGTAAAGAA
CAATTTCTCTCTTTGTATTATAGTTATTTTACATAAGCTACAATCTATAATTCTAAACCTTAATTTCTTG
AAGGGCTTTATAAGCCTCATTTTTCTTTCTAAATAGAGAAGTTCATACACTGCTTTTATGTCCTATATGT
TGATGTGTAAAAAATAATCAAATACTAGTGGGTGAGTAGAATGTAACTACAATATGGTACACACACAGACA
CACAGGATGACTAAACTGTGCACATGAGCTGATGTCCAGAGCAGGGAAAAGCTGCTAAAGAATGTTTGAA
GTAGAGTCAGAATGCAGTTTTGTGGTTAAGACCAATAATTTTTCAAAGGAGCATTATAAGGAGTGTGGTT
ACTTGGGTTGGAGTTGAAAACCAAGCAACAGTTGGGCAGACTTGAAACCAGTTTTGTCTTTAGGTTTCTT
TTCTTAATGATTGGTCTACAATGAGTTAGCCACTCATCGTATTTAAGGTCTTGGTAAAGGAGAGACTTTC
TTTGCCATGTAGTTTATACCTCATGTATGCATTACAGTAGAGAGCTCCAGGAAATACTGCAGGCCTTCTA
CTGGTTTTTATCCTCTATTTAGATAAAAATGAGGAAGAAGTAGAATTATCATAAACAATCCTGTTGGCTT
TTAGTTGAGATATACTACAGAAACATCACCTTTGAATCTGTATATGTAAAAAAAAAAAATCTCAGAGTAA
GATATAAGTTCTGTTGCATTGTTCTGAAGGAATGGGTAATGTCAGAAATGTCTTCATTACATTACATAAA
GTAATACACAGTGCTGTTATCAGATTGCATAGTCAAAGTTGGCAAGTTTGCATATTTACATAGATATCAT
GACCTTCATCATTCATACTTCTTTCAAGAAATGGTCATCTTAATATGGGGTATTTATTTGAGGCATACAC
CATTTATTTTAAGAAGCAGTACCTTTGTTTATTGTAAAACTTCTGGACTAAATTCTTCAATTTTTTCTCA
AATGAATTCAGTTTTTTGTTTTTTTTCTTACCACTGGTTTTTACTGCATAGCGTTTGCCTGAAGAACACC
ACTTTGTTTCCCAAGGCAAGTAGTCACTACAAGGCGAGTTTTGTTCTGTCTATCCCAAGGCAAATAGACA
GCAGCAAACATAGTGTGGAGGGCTGCTGGGTTCAGTAGAAAACCATCAACTATTTCTAATTGGGGGTGTA
TGAAGACAGCTGCATTCTGGACATGCTAAACATCTTGAAATGCTTGGAGTGTAATAAAACCCCAAACGTG
CTTTCTTTTCTCATTTCTTTGCACATGTATTTTAGGCAAAATATAATCCACATGCTGTTGTTCCCTCTCC
TTTTAAATCATGAAAAATGTTGTTTTTATAGGGCTATTTGAGGTCCAGGATGCCTTTTTATCCTTTTTAT
TAGGTTATTTTTATATATAAATGAAAAGAAAAACATAAACAGAAAATACAACATGACATCATGAATGAGG
GCAAGCACAAACTGCCCAATTTAAGTTTGAAGTTATAAACCTAAAATATTTTAAAACAAAACATTTCTCT
TGGTGTTTTGCAAAAGTAATGCTTTCTTCTATTGGGCAGAAATTGCAGCCTGTTGGGATGAAGGAGAGAA
TAGAACTAATATTTATTGAGTAGCTACCATGGCTTTCTGGGACATCTGCTAACCCCTTAATTTTTACAGT
AACCCTAAGTGGTAGGCCAGTCCATCTGCATTTTACAGACAGGAAATGCTTTCAGAGATATTAATTAGAT
GGCTGTAGACCACAGAAGAATTGAAAGTCAGGTCTTCTTGACTTTTCAGCTCATGACTTCATTACTTCTG

FIGURE 1, page 73 of 93

CCCTCCTCATTCTGTTGGGAGATGGGTGGGAGTGTGCCCTCCAGATAATCAGAAAGTCCCATGTTGGGAT
GTGATTTGGAAATAGCTAGTCCTCAGGCCTGTGGACGAAGGCTATTGTAGCCTCAAGAAAGAAAGAGTCA
GCTTGATATTGGCAAGGTGGTTATTTAGTGTGGCAGCTGCATAAGAGCATTGGATAGGTGGTATGATATG
GGATGGGGGTCAGGGTGAGAGCTGCTCACACCTCCTTATTATGGCAGGGCAAAACCAGAATAGTCACAGT
GATGGTGATGTAGGGTAGGTTCAAGAGAAAGCTCATGTTCTTCTAGCATTGAGACTCACAATATTTCAAA
ACAAGTGATTATTTATTCCATTACTATTTATTTGGTGATGGATGTTGCATTTATTTTATTTTCTAACAG
TAGTACATATTTGGTAAGAGTTGTTTGTGACATTCTTTATTTAAATGGATTAAACCCATTTTCTTAATTT
TTTTAAGTGTTTGTCCTGTTATCGAAGATATCTTAAAGTGTTACAGAATGGGAATCATAGCTTTAATGAG
TCTGCATATAAGAGAGTCCAAACATTTTTTTTTTGGAGAGAAGGAAGGTCATTTCAACTGTACTATAGGA
ACGATAGGGCCCATGATCCATGGTATGGCAATAAGTTACTATTTTTTGGAGAATAAATCGCAAAATATGG
GACGTGAAGACTGCTTGGTATTTACACAGGAGTCTAGTTCTTCTGATACTATATATTCTATAAGCTTTCT
CCCAGAAATCCAAAGTTTTATTTAGCTTGTAGCCATCATTGTGCCACAATCTTCCTTCCATGATTTATTT
TTTTCCCATACTGTACTCTTGCACTGAGTCTTTGGCATTGAAAGGGAAAGAGATGAATTATTCAACTCTT
CTTCTATTGAGTGAAAAGCCAATACAGAAAAAAAAAATGCAACAGGCAATTTCATGACTGACATTTTGGAG
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TTCCAGTGAATCTACTGAGGGAACCAACCACCTAGCTTTTTGTAAATAGCACTCCTCAGGGAAATGTTGC
TTTTTTCTTTTGCAGTGTTTCTGCTTTGAATCTTCATAGACTGTATCCCATGGAAGCAGGAATATAATTA
CTGTAGTGCTTACTTTTTTTCATGTCTCTACTGAAGAGCCACCCTGATTTATCTTTTACTCCAAGGTAGT
GTGGAACTTTACAAGGATTTAGATTATATTAGTCATTTTGCTTGGAGATCTCTGCACACTTTTCAACATC
ATTTCTAAGAGCCTTGCCACACTCAGTAAAAGAGGGTGAGGCTTCAAGAATCTCTGTGTACCAACGCAAA
TTAGGCAATTTGTAAGAAGTCCCTAGTAGAGCAGAGTGGAGAGAGGGCTCAGGATCTCGTGAGGCCTGGG
GCAGGGAGGTGGACATGCTATGAGCTCCTTTCACAGTCAACACAAAGTTAACACATCTTGGAGGAAAAAC
CGTTACTGTATAATGGAAGGCAGAAGGCAGGGATGTCTGTGCTTGGTGATGAAGCTATAAGTAGTGAGCT
GATTTATGATGGAGGGGTGAATTGTGCCATGAAAGAGACTCCCCTCAATTTTATTAGCCAGATTACTGCC
CATATGCGGGGTGAGGAGTGAGCATTTTAAGGCATTTCTCTCTGTTTTCAATATATCATCTCTGGATTCA
CTATTACTGGGACTTGTGAATATAGACTAGGGATTAAAACCTGAGTTTGCTTTTAAAAAACTTTATTTTA
TTAAATGAGATTTCTGAGCAACTGATTTCACTTAGTCTTATCAAACTATTCTTACTACTTTTTCGATATG
CATTCTGTCCCTCCTGTGTGAAGGCCACAGGCCCATGGCCCCCATGTCATTGAGATGGAGGTCCTCAAGT
GATGGCGGGATGAATCACCTCTCACTTGCCACCTGCGAGAATGTCTATCACTGATACCTCTCCTTATGTC
CCGTAGCAGCTGCTAAGCTCCCACGTTATTATTGGTGACACTTTCTAGTGTTCAGGAGAGAACAGGATTT
ACTTTTTGAATGCCTCTAAATTATTATAGCAGGTTCATTTGGAATTGCATATCAGAACATTCTTCCTGTT
TATCAGGAAAATAAACCAAGGTCTTGAAACTTGATGTCTATCCATAGTTGGCCCAATATAATTTTGCATG
TGGTTTATTACATTATTTTTCTCCATTGGCTATGAACTGAAGGCATCTCATGGATATTTATTCCACGCTG
AAAAGGTAGTTAGATGCTGTGTGGTAAAGTCGAGACCAGTATATTGGAAGAAAAGAGACACTCCATCTAA
TAATCTTTCATAGTCTTCACATTCATTGAGAAGGTTACTTGATAACCTTTCCTGCACACTCTCTCCCAAC
CCTGACCCAGGAACTTGCAGAGCACACTGTGCAACAGATCTAATAACCCTTGTCTGCAGGCAATATGCAC
AGCTGGGAAAGATAATTAAATAGACTCTTTTTGAGAGGTCTACAACATTTCAACGGAAGGATCGAGCAAT
CCGGCTGGCCTCCGACTGAAAACTATTACCAACAGACATACTTCAGACAGATTCCATGATCACCATCCTT
ATGTGGCACAAGTGCTTATGGGGAGCTTCTTTGGCTTCCAAAAGGCCACTAAAACTGTCAGACCTAAATA
ATACTGGAACTGTAAAGTGGGAATTAAAAATTATAATTCCATTTAACATGTAACGTTCTCATCAGAAAGG
GGCCTTTGGTTTTCCATATTGATCGGTTACATGGTCAGCTGCAATTGTAACTCATGAGACACACCCAGAT
ATCATCCTGCGTGATTCTTTTTGAGGTTTATTTAGGGTGTTAGATAATCCGAGGTAGGTTTCATCATGGG
TGGCAATATTACATATAGCAAATGTCATGAGAAGAGAGACAAAGCCTCCCTTTTGAATGTTAACATTTAT
GCAATAAGTTTAATGTACCGTGTAAGTTTACATTACTATTATGAGACTTAACCTAAAAAATTGGGGTGAA
ATCTTAAAGAATTATGAAATTAAGAAATGAAACCAGAGGGCTTTCGTTTTAAGTACTGATCACTTAAACC
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GATGTTTCCTTGAGAGCAAGACTAGTTCCTTTTGACCCAGTACATCCTACAGGTAAATCACTGCATGCTG
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TTACTTATCCTTATAAACAAAGCCACCCACTTTCTCATTTTTCCTGATGCCAAGTCCTTCTTTACATGAG
TGGAATCCACTCTTTTCAATGGAAAGACACCTGCTCTGAGACAGGCTACACTGTCATGAGCCTTGGCATG
GCTGAGTGATGTAGTGGAAGGTGCAATAAATTTAAACTTTAAAAATGCAAAATTTGATGGAATCATGCAT
CTTGTGCCTACAGTGAGTATATGGTCTAGCAGGATTTACAGATACATGCATGATTAATTTGAATACAGTA
TAGCAAAATGATCTGTTAAAAAACACATGAAAGATGTGCAACCTTATTAGTCATTAGGAAAATGCACAT
AAAACCACCGTTCCTGTGTGATACCTCTGTACGTCTATTAGAATGTATAAAATTTAAAAAGACTGAACAT
AGCAAGCACTGGTGAGGTTGTAGACCAACTGGTGCTTTCATGTTTTGCTGGTGAGAATGTAAACATTACA
ACTACTTTGAAAACAGTTTGACAGTTTCTTAAAAAGCTAAAACATCCACCTGGCATGCTATATACAGATA
TCCTACTCTTACGTATTTAACCAAGAGAAATAAAAGCATATATCCATTCAAAAACTTGTAAATAAATTGC
TCCTAGCAGCTTTATTTGTAATAGCCAAAAACTAGAAACAACCCAAATGTCCAATGAAAGGATACATCGT
ATTTATTTATAGGACATATCCATGCAATGGAATACCACTTAGGAATAGAAAGAATCAACTGTTCATCATA
CATACAACCACATGGCTAAGTCTTAAAAATAATTATGCTTAGTTAAGAAGTCAGACAAAAAGGTAAGAGA
CTGTTAGGAGCTGAATTAGCGGGTTAACAGTGGCAATGAAAAAGGAGAAAATTATAGCTACCTCAAGATA
GAATTGATGAGCTTTGATTATGAAATGATGGTAAGAGAGAGGGCCATAGACTCTGAGGTCTGTCTCTAGC
TTTGGTTTCCCTATGTGGATCATTATCTATTTGGATATAAGAATTATCTGAAAGATGATACTTAAGCATG
TAAGAAATGATAAGCTACCTGTTTAATGATGAGCTTTTGTTACCTCCAAGAACCCCAAGAAGAAACATCC
TGTAAGCAGACCATTCATACTTGATTGTTAAAGGAAAACAAAATTCCATTTTGTCTTTTTCATCAACACA
AGTATAGCTGGCTAATAAAAGTGTAATATTCATGAGAGAAAAAGAAAAGAACACGCACACACATACACTC
AACAGGATTCCTAGAGTCATTCCCATGGATAAGAGGGAAGGAAAGGTTGAGGGCAAAGAGAGAAGGGAAG
GAAACAGACTATGATGGGATATCTTAGGGCAAAAGAATAGGGGGCTGATTTGGAAGGCAGCAAACTTCAT
GGATACTTGATTTATTTAATGTCCCTGTCACTCTGGCGTATCTTAATGTGTGTGGTGTGTGATTTATTTA
GTCACTTGATCCAAATTCTCTAATTAAGTGGAGCTCAGAAGATATAGTGTCCATTGTGGTCAAGGGCACA
GGTTTTGGCTTCAACAGACAAATAAGCTCTCTGAGCATCTGTCTTCTCATCTGTACAATGGGAATATCAG
TTCCTACCTCTTCAGGTTGTTGTATTCATAAATAAATTGTGTACAAGAAACATTAGGATTGCTTCTTACC

CGTAGTAAGGGCTCAACAAACCTTCTCCTCCTTCTCCTCCTCCTTCTCCTTCTTCTTCTTCCTCCTCCTC
CTCTTCTTCTTCCTTTTGCTTTTCTCCTTCCTTCTTCCTTCCTTTCTTCCTACCTCCTTCTCATTATTGT
TATTAGGTAACCACAATATTATCAGTAATGATTGGAGAAAGCTTTAATCTCCTAGTTCACCATTAGAAAA
CAAGAACACATTTTGGTGGTTATTACCCGAAGTAATCATAATGTCACCTTTTTTTCCATCTGACTCATTA
TCCCAAGTGATTTATTTATATATGGAGTTTTCTGAGTCTTTCTTTTACATATTACAAAAAAAGAGTGTGA
TTTAGGGACGAAGCAAAGAAATAAAAATTTAGTGACTTTCATTCTGCCTGTGCCCCAATTCCTATTGGGC
ATAAGGCAAGTAATTTAAATTTCTTAGCACCTTAGCATCTTCTACTCAAACAGAAATGAGGAACAGTCAC
AGGTTACTATTATAGCTGTCTAAGTAGAAGGCACACAAGTTTTCACACTGAGTATAACACTTTATAGAAA
GCTAAGTGTGTTGCTCAAGTTGGTACATTTCTGTAGATGTGACACTATGGCACTAAGAAACTTAATGCCA
CATTGAAATTCATTGAGATAGCTAGACTTTAAAAATAATTACTTGACTTCACTATAAAGTATGTTCGTAT
TGCATTTACTCCATCTAGTAGAAAATAGACCTTGTCAGTTCAAATCCCTGTTGCATTAATTTCACCAGTA
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ATGATCAGGTCCACCTTCTAGAATGTGCCTGGCTAGAGATCCTGATGATTGGTCTCGTCTGGCGCTCCAT
GGAGCACCCAGGGAAGCTACTGTTTGCTCCTAACTTGCTCTTGGACAGGTAAGTGACCTGGCTGTAGCTT
AGGAGTAGCATGTTCTTTACGATCATAGTTCATTCATGAAACTATTTTATTCATCTCTCGGTGAAGCTTC
AGAGAACTTTATTAGGTATGTTTACTTAACAAAAGAGTGCATTGGGGGTGATGAAGCCTAGTCAAATTCA
CAGAAAGCTAAGGATAACTTTCTGCTAGACATTACCTCAGAAGAATTCTATTATTTCTAATACACACACA
CACACACACACACACACACACTCACACTCTCTCTCTCTCTCTCTCTGTCATTATGAATGGTAATTTTCTA
ACTCCATCTTCAACTTGTATCATATAAAAATTATAATAACCTCTCTTTAATTAAAATCTGTTGTTGCTTC
TTGTACATCCATACCACAATAGCCTATTCATTTTCTTCTCCAATTTTCCCATCCGTAAAATGAAGAAATT
TGACCAGAGTTCTGAAGGTCACATTCAGGTCGACAAATTCATTTTCATGTTCAAATATGTTACCTTCTTT
AACATACCATTCTGGGGTTGCCTTGGAATGTGGGTCCCATTGTTTTTTTTTTTTCAGTCATTGCTTAGAG
TCATAGAATTTAGATATTACTCAATAGCAGCTGCCACTGATAGAGTCTCCACCCTGCACCAGCTGTGATG
CTAAACACTTTACATATATTATCTCATTTAATCATCACCGGACTCCTAGGAGGCAGGAATGTCATCATCC
ATGTTTTACCAGAAAGGAAACTAAATCTCAGAGACATCCTGCTACTTGCAAAAAGAGGAAAGCTCACTAA
ATGGTGGAGCCAGAGTTCAAATTCAAGATCTTTCTGGCTCCGGTATGCTCTGTTACCTCCTGTGCTGGGC
ACATGGTCTTCCCACTCTCATGTTCAGTGATGCCTCCTTTGGTCTGCTGCCATAGCATTCTGTTTTCCAG
GTAAATCTTGTCTTTGTGGGCTACATAACATTTTGGATGAGAAAGAACCATTTTGTTGTTTCTTGCAATC
CTATTTTGCCTCCGTGCCAAGCAGTCTAAGGCTGCCAGGCTGCCCACAGTGCATCTCTGCATGGTACTTT
ACTTCAGAGCATTTCACTATCTTTCTACACCTGCCAAGTGCCTGGAGCAGAGTTGCAGCAAAATTTATTT
AAGTACTGGAGAATTGTACAAGGTGTTGGTTATTGTTTTGTCATTTTGTGTTAACACAGCTTTTGAAAAA
CAGTGGTGATACAGTTTAAGAAGCATATTTTGCTGTCTGTGGAATATATTTTGATATCACAGTTTCACAA
AATTATCAAGAATGGCCACTAGTCTTGTTCCTTAGAACTGTACTCACAATGTATTCTGTCAGCCTTATAG
AGGATGTCTTTACCGTGTTCTTTCCTTTCCATTCCTTGTTTCCTTTCCATTTTTTCCTATCTCATTTCTC
CTCTCTTTTCCTTTGCTTTCCTCTTTCTTTCTTTCTCCTGTCCTCTTAATTTTTTTGTCTTATAGCAGTG
TGGTTTTGTAACCAAGTGATATCAAGTTTGCAAATGAAAATCTTAGACCACACGTAACATTTCCCTGCCT
ACTGCCTGGAGTGTCTACCATGTTTAGGTTTTGGACATTCATAACTCATTTGCTCCTTGATTTCCATCC
TCATCTGTATCTATCTTCTTTTTTAAAATTTAATTCAATTTTTATAATGTTGACACAATTATGCAGATTC
ATAGGGTACACAGTGATGTTTTGATACATATAATGTGTGGTGATCTTATCTATCTTCTTGAGTACACACT
TGCTTGAGGACAGTCATCAAATAATTGCATTTTGAATATGTGAAGGTTTTTGACATTACTGCACCCAAAA
AACTCATATTGCCAGTGAGGTGATATGGCCTAGGATTTTATCAGCTACAGCCTTCTCTTTCCTTTCTGTA
CACTCCAGTGGTGGCTAATTTTCTTTCCTCTCTCACAGAAGTATGAATGACTAAAAGTTCTCATCTCTAT
TCATTCCTACTTTCTAAAACTTCAGATCGGAAATTTGAATTACCTCTAGACCAGGATTTGTCAGTCTCTT
TACTATTGACATTTTGGGTCAGATCATTCTTTCATTCTTTCTTGGTTGAGGGGTTGATATTGTTTGGTGT
GTCCTCATCCAAATCTCAAATTATAGCTCCCATAGTTCCCATGTGTCATGGGAGGGACCCGGTGGGAGGT
AACTGAAACATAAGCAAAGGTCTTTCCCTTGCTCCTCTCATGACAGTGAATTTCTCATGATATCTAATGG
TTTTATAAAGGGGAGTTCCCCTGCACACGCTCTCTCTCTTCCCCGTTGCCATGAAAGATGTGACTTTGCT
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TAAATTACCCAGTCTCAGGTAGGTCTTTATTAGCAGCTTGAGAACAGACTAATACAAGGGGCTGTCTTGT
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AACAAACTATCTCTCAGACCACAGTGCAATCAAACTAGAACTCAGGATTAAGAAACTCACTCAAAACCGC

FIGURE 1, page 78 of 93

TCAACTACATGGAAACTGAACAACCTGCTCCTGAATGACTACTGGGTACATAACGAAATGAAGGCAGAAA
TAAAGATGTTCTTTGAAACCAATGAGAACAAAGACACAACATACCAGAATCTCTGGGACACATTCAAAGC
AGTGTGTAGAGGGAACTTTATAGCACTAAATGCCCGCAAGAGAAAGCAGGAAAGATCTAAAATTGACACC
CTAACATCACAATTAAAAGAACTAGAGAAGCAAGAGCAAACACGTTCAAAAGCTAGCAGAAGACAAGAAA
TAACTAAGATCAGAGCAGAACTGAAGGAGATAGAGACACAAAAAACCCTTCAAAAAATCAATGAATCTAG
GAGCTGGTTTTTTGAAAAGATCGATAAAACTGATAGACTGCTAGCATGACTAATAAAGAAGAAAAGAGAG
AAGAATCAAATAGATGCAATAAAAAATGATAAAGGGGATATCACCACTGATCCCACAGAAATACAAACTA
CCATCAGAGAATACTATAAACACCTCTACACAAATAAACTAGAACATCTAGAAGAAATGGATAAATTCCT
CGACACATACACCCTCCCAAGACTAAACCAGGAAGAAGCTGAATCTCTGAATAGACCAATAATAGGCTCT
GAAGTTGAGGCAATAATTAATAGCTTACCAATCAAAAAAAAGTCCAGGAGCAGACGGATTCACAGCTGAA
TTCTACCAGAGGTACAAGGAGGAGCTGGTACCATTCCTTCGGAAACTATTCCAATCAATAGAAAAAGAGG
GAATCCTCCCTAACTCATTTTATGAGGCCAGCATCATCCTGATACCAAAGCCTGGCAGAGACACAACAAA
AAAAGAGAATTTTAGACCAATATCCCTGATGAACATTGATGCAAAAATCCTGAGTAAAATACTGGCAAAC
CGAATCCAGCAGCACATCAAAAAGCTTATCCACCATGGTCAAGTGGGCTTCATCCCTGGGATGCAAGGCT
GGTTCAACATATGCAAGTCAATAAACATAATCCAGCATATAAACAGAACCAATGACAAAAACCACATGAT
TATCTCAATAGATGCAGAAAAGGCCTTTGACAAAATTCAACAACCCTTCATGCTAAAAACTCTCAATAAA
TTAGGTATTGATGGGACCTATCTCAAAATAATAAGAGCTATCTATGACAAACCCACAGCCAATATCATAC
TGAATGGACAAAACCTGGGAGCATTCCCTTTGAAAACTGGCACAAGACAGGGATGCCCTCTCTCACCACT
CCTATTCAACATAGTGTTGGAAGTTCTGGTTAGGGCAATCAGGCAGGAGAAGGAAATAAAGGGTATTCAA
TTAGGAAAAGAGGAAGTCAAATTGTCCCTGTTTGCAGATGACATGATTGTATATCTAGAAAACTCCATCG
TCTCAGCGCAAAATCTCCTTAAGCTGATAAGCAGCTTCAGCAAAGTCTCAGGATACAAAATCAATGTGCA
AAAATCACAGGCATTCTTATACACCAATAACAGACAAACGGAGAGCCAAATCATGAGTGAACTTCCATTC
ACAATTGCTTCAAAGGAATAAAATACCTAAGAATCCAACTTACAAGGGATGTGAAGGACCTCTTCAAGGA
GAACTACAAACCACTGCTCAACGAAATAAAAGAAGATACAAACAAATGCAAGAACATTCCATGCTTATGG
GTAGGAAGAATCAATATCATGAAAATGGCCATACTGCCCAAGGTAATTTATAGATTCAATGCTATCCCCA
TCAAGCTACCAATGACTTTCTTCACAGAATTGGAAAAAACTACTTTAAAGTTCATATGGAACCAAAAAAG
AGCCCGCATTGCCAAGTCAATCATAAGCCAAAAGAACAAAGCTGGAGGCATCATGCTACCTGACTTCAAA
CTATACTACAAGGCCACAGTAACGAAAACAGCATGGTACTGGTACCAAAACAGAGATATAGACCAATGGA
ACAGAACAGAGCCCTCAGAAATAATGCCATGTATCTACAACTGTCTGATCTTTGACAAACCTGAGAAAAA
CAAGAAATGGGGAAAGGATTCCCTATTTAATAAATGGTGCTGGGAAAACTGGCTAGCCATATGTAGAAAG
CTGAAACTGGATCCCTTCCTTACACCTTATACAAAAATTAATTCAAGATGGATTAAAGACTTAAATGTTA
GATCGAAAACCATAAAAACCCTAGAAGAAAACCTAGGCAATACCATTCAGGACATAGGCATGGGCAAGGA
CTTCATGTCTAAAACACCAAAAGCAATGGCAACAAAAGCCAAAATTGACAAATGGGATCTAATTAAACTA
AAGAGCTTCTGCACAGCAAAAGAGAAACTACCATCAGAGTGAACAGGCAACCTACAGAATGGGAGAAAAT
CTTTGCAATCTACTCATTTGACAAAGGGCTAATATCCAGAATCTACAATGAACTCAAACAAATTTACAAG
AAAAAAACAAACAACACCATCAACAAATGGGCGAAGGATATGAACAGACACTTCTCAAAAGAAGACATTT
ATGCAGCCAACAGACACATGAAAAAATGCTCATCATCACTGGTCATCAGAGAAATGCAAATCAAAACCAC
AATGAGATACCATCTCACACCAGTTAGAATGGTGATTATTCAGAAGTCAGGGAAAAACAGGTGCTGGAGA
GGATGTGGAGAAATAGGAAGACTTTTACACTGTTGGTGGGACTGTAAACTAGTTCAACCATTGTGGAATT
CAGTGTGGCGATTCCTCAGGGATCTAAAACTAGAAATACCATTTGACCCAGCCATCCCATTACTGGGTAT
ATACCCAAAGGATTATAAATCATGCTGCTATAAAGACACATGCACACGTATGTTTATTGCAGCACTATTC
ACAATAGCAAAGACTTGGAACCAACCCAAATGTCCAACAATGATCTGGATTAAGAAAATGTGGCACATAT
ATACCATGGAATACTATGCAGCCATAAAAAAGGATGAGTTCATGTCCTTTGTAAGGACATGGATGAAACT
GGAAACCATCATTCTGAGCGAACTATCGCAAGGACAAAAAACCAAACACCACATGTTCTCACTCATAGGT
GGGAGTTGAACAATGAGAACACGTGGACACAGGAAGGGGAACATCACACACCGGGGCCTTTTGTGTGGTT
GGGGAGGGGGGAGGGATGCATTAGGAGATACACCTAATGTAAATGACGAGTTAATGGGTGCAGCACACCA
ACATGGCACATGTATGCATATGTAACAAACCTGCCCATTGTGCACATGTACCCTAAAACTTAAAGTACAA
TAAAAATAAATAAATAAATAAATAAATAAATACTAGTTTGGCTGCATTGCTTTGATTTTCTTCTTTAGGG
GCCTGTTCATACATACAAAGGATACCATTTACCTGTCTTCTATATGACTTTCTCTTAAATCCTTTCATTC
TTTTGTTTTAATTTTTATCTTCACATCCTTTATTTCTGTCACTGTGCTGTCCATAGAGTTTGTCTGCTGT
GTGTCCTTATAATTAAGTCTATGTTCTGAATGTTTTTCCTTTTTTAGAAATTCAGTTCTAAAGTGTTTAA
TTTCTCGTATTTTTTTTTCTGTTGCCTCACCATATCATTTCTGAGTTTTCTGTTTCTGAAATGTGCAACT
AACTCTTTCAAAGCATTGACCAGATTCTTCAGTCTTTTTAATTCATTCTGAAATAACTGGGCTACAGTTT
CATCTGCTTTGTGGACAGAAGTGCCACAAAGAGCCGAATTGTCAGTGCAGACCCACATGAATCATAGATC
TTAACGAAGTTTTTACTAACGACTAGCAAAGGATACAAGCTAAAAATGGGTACAAGCAAACACAGCATCA
TTCATCACTGTAAAGACTCTGAACTATCACATGGAACTTCAAAAGGATTCTTCTTCTTTGCTGCAATGTG
TTTTGATTTTTGGAGTGATAGATGTTTGCTAACTACGCACGTGACAAAAATTTGCTTAGAGGAAGCCATG
TTAGTTTTGATGCTACTCAACTTTGTATTTTGTTAGTCATGAGATAGAAAGCCTGTGAGATTACGTGCCC
TTCTTTTAGCAGCTGCATCCCATAAAACTAAAAATTCCAGTTTTGTTTAAACCATGAACAATTTAGTCAG
ACTTAATATATCCTATTTAAAACATTCTTAGATAAGAACTTCCTTTGTTATTTTGCTAATATACAATCCC
ACCAAATGTCTACAAGAAGGGCTAGTTAATCAATATACCAAAGATCAAATCTATTTATATGAACCACAAA
TACAAAACATAATTATACATATATAATTTTATATAATTTAATTTATAATTATATACATTTTATAGCAGCA
ATCAAAACTATCATGTATTTTGGGATGAATTTAATAAAGAAATAGCAGGAGCTCTGTAGAAACAAGTATG
AACTTCTATTGGAAGACAGTAATATCATAAAACATTAAAAAGAAAGCTATACCATGTTTATGGTTAGGAA
GATTCATTATTGAAAATACATCAATTCTTGATAAATTGGTCTATAAATTCAGTGCGTGTCCAATCAATAT
ATTTAGCTCATTTAAAATGTATATGGAAAAGGCTAAGTACCAAAGATAATCAAATGCTCTTCGAAGATGA
AAATTAAAGTTGAGAGATGGGGTAAAAAACTATAATTCAGTTCTAAAGTCATAAAGCTATAATAATTAAT
ACAGTATGGCATTGGCATAGAAATAAGCACATTGACTAAATAAATAGAAAATACAGTTCAGAAACCAACC
TCTACATTTATGAAAAACTGACCTATATCAGAACGAGCATTGAGACTACAGGAGAACAGAGGAACTAGTA
AGTTAATGGTCCTGACACAATTGATATCTACATAGAAAAAAAAACTTAATCCTTCTTTACTCTATGTAAA
AACAATAATTCCAGATGAATGTAGGACTTAATGGAGAGCCAAAACTAAAACTTTTATAGGAAAACATAGA
AAAATACCTATCTCAGGGTCGGGAATTAGGTCTTCAACATGGCACCAAAAGTACTAACCATAAAAGAAAC

FIGURE 1, page 79 of 93

ATTAATAAAGTCAACCTTTTTAAAATCAACAACTTTAATTAAAAAACCAGGGCCAGGCGCGGTGGCTCAC
GCCTGTAATCCCAGGAGGCCGATCACGAGGTCAGGAGATCGAGACCAGCCTGGCCAACATGGCAAAACCC
CGTCTCTACTAAAAATATAAAAATTAGCTGGGCGTGGTGGCGGGTGCCTGTAGTCCCAGCTACTTGGGAG
GCTGAGGCAGGAGAATGGTGTGAACCTGGGAGGCGGAGCTTGCAGTGAGCTGAAATCGTGCCACTGCACT
CCAGCCTGGGCAACAGTGTGAGACTCCATCTCAAAAAACAAAAACAAAAACAAAATCAAAACAAAAAACA
AAACACAGGTTGCTGGAAAAATGGTTACTTATTTTTATTATGCTTTATAAAATATACAGTTATATTATCA
AACTTCTTTTGTAAGAATCAAATATTATGCTGAGAATATGGCAAGAAAAAAGAAAACAACCTCCACCACT
CATAATGGCATTCCCTTTACCCACCATCAACTAAGTCAGGAACCTGCGTCACTTTCAAGTTTTCTGAAAT
GTGGACTGAAAATACTTGTGGAGGGCCCTCACAGATGCATTTAGAAATGGTATGTTCTGGAAAATGGAAC
TGAAATGTTTTAGCGAGAGTCATGGGCCCAAACCTTGAAATAGAGGTTGGTGGAGTTTTCTATAGTATGT
AATTACAACACAATAAGACTCAAAAGCATTTCAATAAAGTGTGGGTGGAAGACAAGATACTGCTTCAAGG
GCTTCATTAGCTTTCTGCAGACTGGAGCTCTCCAAGGCATGGGGAGGAACCCTGTTTACCTTTGGTTCAG
AATCAGTTTTAACCATCATTGAGGGCTAGGTCAGAGTGCAGCATTAAGTCCTTGGGAATACACTGGGTGG
GGAAAGAAAAGAGAGCAATGTTTTTCTAAAAGCCCAGAAATGGGCTTACTGTGTTTACCAGTTGTTTCCA
GGATAATGTATTGCAGCGCCAATTGCTGATGAGATGGTAGGATTATACTTCAGTCCCTGCTTTACATTTA
TTTCTTAAAGAAGCTTCTGGTAAATTAGAGCAATAGCATCGGCTTAGTTTAGTGTTGTTCTGTTGGACTA
AGGATATCAGTTCTATCCGTATGGGCGGGCCTAAAGCCTGGGAAATATTTAATGAAGGGAGAGAGGGGGA
GAGAGTGAGCATGCAAAAGAGAGAGAGAAAAACAAATAACAAAACAAAAACCAAGACATTTCCCTTTATA
GTAAGAATGATGAGGAAAACATGTTTAGCCATACAAGATATCAAGATAATCTCTTATTTCTTTCTTGAAA
ATGCAAGTACAAATGCCTGCAAAGATAAAATATCCTCTGGATGGAGTGGAAAGGTTCACCAGGCCTCTGA
AATCACGTGAATGATGTTGCGCTTTGCTGTTAATGAAGCTCGGTGCATTTTTCATTTCAGTTTCTACTAA
GCATTTATGAGCTATTACCCTTCCCTTCCCTAAACTGCGTTGTTTTTTAAAAAGCCTTAGAGGCATTCCT
TCTAGAAAATAAAGGTAAGTGTTAAGTGGTGATAATTTGGTAATAGGTGTCATGCTTGTGGTTCATAATG
TGTTACCCTACACATTTTCTCAATTATCCCTAGAACAGCTTTTTGAGGATATGAAGTTAGACCTTACAAA
GCACATCTTTCTGCTGGAAAAATGAGGTTTATAGTGGTTAAGTTTAGTTGCTTATGATCACAAGGCTAGA
GAGTGGCTGGAATCAAGACTCTTCACCCTGATTTCAGTGCTTTTTCACTCCACCATTAATATTTATTGTT
GATAAATAATATCAACACTTTCCTAGGTGTATTAGGGTCATCTAGAGGGACAGGACTAATAGGATAGATG
TATATATGAAAAGGAGTTTATTAAGGAGTATTGACTCACACCATCACAAGGTGACGTCCCACAATAGGCC
ATCTGCAAGCTGAGGGGCAAGGAAGCCAATCTGAGTCCCAAAACCTCAAAAATAGGGAAGCTGACAGTGC
AGCCTTCAGTCTGTGGCCAAAGGCCCAAGAGCCCCTGGCAAACCACTAGTGTAGGTCCAAGAGTCCAAAA
GCTAAAGGATTGGAGTCCAATGTTTGAGGGCAGGAAGCATCCGTCATGAGAGAAAGATGGAAGCCAGAAG
ACAGCCAGTCTAGTCCTTCCACGTTCCTCTGCCTGCTTTTATCCTAGCCACGCTGGCATGATGATGACAT
GGTGCCCGCCCAGATTGAGGATGGGTCTCCATCTTCCAGTTCACTGACACAAATGTTAATCTTCTTTGGT
AATACCCTCACAGACACACCCAAGGACAGCACTTTGCATCCTTCAATACAATCAAGTTGGCACTCAGTAA
TAACCATCACAAGTCCACACCTTGTCAACTTGATCCCACATACATCTCCTTAAATCATACATAATCTCCA
AATACAGACAATAATGTCATAATTACACCGAACATAATACAACTATCGTTCATACAACCAGAAATGCACC
AATTCCCAAACCAAATGTTATTACATAAAGTTAACAACACTTAAATGCTGATATGAAGTCAATAAATACT
TTTTTTTTTTAAAAGATGGAGTCTTGCTTTGTTGCCCAGGCTGGAATGCAGTGGTGCGATATTGGCTCAC
TGCAACCTCCGCCTCCTGGGTTCAAGCAATTCTCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCAC
CCACCGCCACACCTGGATAATTTTTGTATTTTTAGTAAAGACGGGGTTTTGCCATCTTGGCCAGGCTGGT
CTTGAACTCCTGACCTCGTGATCCACCCACCTCGGCCTCCCAAAGTGGTGGATCCCAAAGTGATCCACCC
ACCTTGACCTCCCAGGTTGTAAGCCACTAAATCTTATGTCACATGATACAGGAAAAAGAAAGGAAGTAAA
ATGAAGATATTGTCTTAGTACAAGTGTATACATGCAGAAAGATGTTCTTAACAAAATAAGGAGGAAATAC
TCATGACAATTACAGTAACCTGGTTGCTGCAACTCATCACATGGTCGTAGCTGTTATTGATGACTACCTT
CTTCTACAACCCATTCTGTTTTCCCTTTGCCTCTAGCAAGTACCTCAGCAGGTCATGGTTCTTTACCTGG
TGGAGTGTCCCAAACCTTCATTCCTGAAGGGTCTGGGCCATTTGTAGTCCTGCCTGGATCGAGTTGTTGT
CATTTTTTATTGACCTTAATCACAGGGCATGGTAATACTAAGAGACACCCTAAGGAATTTCCTGTATTCC
ACACATATTCTTCCTTACCTTCATTATGGAGTAGCAGACTGAGTTCATCTTGATAGGCTAAGTCAGTCAC
CCCAGCCAACACTAACTCCTTTCTTAGCCTGTTGACTTAGAGGTAGGAGGAGCCCGAGATTGCAATCTTA
ATTTCCAGTTTAATGAAATCATTATTGTGTCTCCTGGCGGCAACATTCATCGCCCCTGGAACTGAGACTTC
TAGGCCAGCAGAACGTAATGCTGTGGAACAAGAAGCAAAAATTTTACTAGCGGGTCTCTAGGGGTGATGG
TGAGTGGTGCCACTTCCATTTCCACCCCTTGATTCCTGGACCCATGAATCCTGGCTATGGGAGAAACAGT
ACCAAATACTGGACACTGATCCGGAGCCTACACAGCCTTCTCGGAAAACTTTGCCCCAGCCCTGCAAAGTA
TTGTCGCCTAGTTGGCATTGTAATTGTGACTTCAAAAGGCCATTCCACCGTTCTATCAATCCGGCTGCTT
CAGGATGATGGGGAACAGGGTAAGACCAGTGAATTCCATAAGCATGAGCCCACTGCTGCACTTCTTTAGC
CATAAAGTGAGTGCCTTGTTCAGAGGCAATGCTGTGTGGAATGCCATGACAGTGGGTAAAGCATTCCATA
AGTCCATGGATGGTAGTCTTGGCGGAAGCATTGCCTGCAGGATAGGCAAACCCATATCTAGAGTAAGTGC
CCATTCCAGTGAAGACAAACCACTGTTCTTTCTGTGATGGAAGAGGTTCAGTATAATCAACCTGCCACCA
AGTAGCTGGCTGATCACCCCGAGGAATGGTGCCATATCGCGGCCTCAGTGTTTGTCTCTGCTGCTGGCAA
ATTGGGCACTCAGTTGTGGCTGTAGCCAGGTCAGCCTTGGTACGTGGAAGTCCATGTTGCTGAGCCCGTG
CGTAACCTCCATCCCTGCCACCACAGCCACTTTGTTCATGGGCCTATTGGGCGATGACAATGGTGGCTGG
GGAAAGAGGCTGAGTGGTATCCACAGAACGAGTCATCCAATCCACTTGATTATTAAAATCCTCCTCTGCT
GAGGTCATCTTTTGGTGAGCACTCACATGAGATACAAATATCTTCACAGTTTTTGACCACTCAGAGAGGT
CCATCCATCCACATACCTCTTCCCCAAATTTCATTGTCATCAGTTTTCCAATCATGCTTCTTTCAAGTCC
CTGACCATCCAGCCAAACCATTGGCTACCTCCCATGAATCAGTATATAGTCACACATCTTGCCATTTCTC
CTTCTAAGCAAAGTGCACAGCCAGGGGCACTGCTCAAAGTTCTGCGCATTGGGAAGATTTCCCCTTCACTG
CTGCCCTTCAGGGATGTCCTAGAAAGGGGCTGTAGTGCTGCAGCTGTCCACTTTTGGGTGGTGACTGCAT
CATGCAGAGCCATCTGTAAACCAGGCCCTTGTCTTCTCTTCCTCTGTCAGCTTATCATAGGGAACTCCCC
ATGAGGCCATCAGTGCAGGCTGGGGGAGAGAAGGCAGGGTGGCAGGAGTGGGGACCATGGGCATTTGAGC
TACTTCCTCATGTAAAGTACTTGTTCCCTCAGGACTTGCTTGAGCCTGATCATGTATATACCACTTCCAT
TTGATGATGGAATGCTGCTGTGCACAACCCACTTTATGGCTAGATGGGTCAAAAAGCATCTAGTTCATGA
TAGGCAATTTAGGTAGCTTGGTGATTTGATGACCTGTAGTCAAACATACAGTTTCTACCAAAGCACAGTA

FIGURE 1, page 80 of 93

ACAGGCCAAGAGTTGTCTCTCACAAGGAGAGTAGTTATCTGCAGGAGATGCAGGGCCTTGCTCCAAATTC
CTAGAGGCCTCCCCTGTGATTGACCTATAGGGGCCTGCCAAAGGCTCCAAACAACATCCCTATCTGCCAT
TGACACTTCAAGCACCATTGGATCTGCCAGGTCATATGGCCCAAGTGGCAGAGCAGCTTGCCAAGCATTC
TGGACCTGTTGCAGAGCCTTCTCTTCTGGATCCCACTCAAAACTGGAAGCCTTTCAGGTCACTTGATAAA
TGGGCTGGAGTAACACACCTAAATGAGGAATGTGTTGCCTCCAAAATCCAAATAGGCCCGCTAGGCATTG
TGCCTCTTTCTTAGTTGTAGGAGGGGCCAAAGGCAGCAACTTATCCTTCATCTTAGAAGGAATATCTTGA
CAGACCCCACACCACTGGACCCCTAGAAGTTTTACTGAGGTAGAAGTTCCCTAAATTTTAGTCAATTTTA
TTTCCCAACCTCTGGCACACAAATGTCTCACCAATAAATCCAGTATGTTTGCTACTTCTTGCTCATTGGA
TCCAATCAGCATAATGTCATGAATATAATGGACCAGTGTGATATCTTGTGGAAGAGAAAAACTATCAAGA
TCTCTCCAACAAGATTATGACACAAAGCTGGAGAATCGATATACCCCTGAGGTAGGACAGTAAAGGTATA
TTGCTGGCCTTGCCAGCTGAAGGCAAATTGCTTCTGCTGGGCCTTATGGACAGGAATGGAGAAAAAGCCA
TTTGCCAAATCAATGGTTGCATACCAGGTACCAGGAGATGTGTTAATTTGCTCAAGTAATGAACCCATAT
CTGGTCCAGCAGCTGCAATTGGAGTCACCGCTTAGTTAAGCTTACAATAATCCACTGTCATTTTACAAGA
TCCATCTGTCTTCTGCACAGGCCAAACAGGAAAGTTGAACGGGGATGTGGTGGGAATCACCACCCCTGCA
TCTTTGAAGTCCTTGATGGTGGCACTAACTTCCTCCAGGGAGGCAATGTTGTGTTTGATTTACTATTTTT
CTAGGTAGAGGCAGCTGTAATGGCTTCCATTTGGCCTTTCCCACCATAATAGCCCTCACCCTACCAGTCA
GGGAGCCAATGTGGGGGTTCTGCCAGCTGCTAAATATGTCTATGCCAATTATGCATTCTGGCACTAGGGA
AATGACCACAGGATGAGTCTGGGACCCACCAGCCCCACTGTAAGTTGGACCTGAGCTAAAATTCCATTAA
TTAACTGATCTCCAAAAGCCCCTACTTTAACTGGAGGACCACGTGATGTTTTGGGTCCCCTGGAATCAAC
GTCAGCTCAGAGCCAGTGTCCAGTTGTCCCTGAAATGTCTGATTATTTCCCTTTCCCCAGTGCACAGTTA
CCCTGGTAAAAGGCCAGAGGTCTCCTGGGGGAAGGATGGGAGAAAGAGTCACTGCATAAATTGTCAGCAA
TGTAGTGGGGTCCTTCCTCAAGGGGACCCAGCCTCCCCTTCATTCAAGGGGTTCTGGGTCTATAAACTGG
TTCAAGTCTGCAAATTGATTGAGGGGCCGTGATTCTTTGTATAATTTTTAATTTAAATTAGTCTTTTGTC
TACTTGACCTGGAAGTTTTCTGCTTATATAAATTAAGCAAGAATGCAGTAGGCTTCTTGTCAATTTCACT
TTTTAGGAACACTGAGATTAAGTAGCCAATGCCAGAGCTCTACACAAGTCAGACTATTCTGATTGTTGCC
TTGCCTCCGCTGACCTTTACGGTAATTGCACCCACCTTGCCTTGATGCTTGAGTGCCACCACTTCGCCCA
TGCCACCTCAGGATCCAATTATTACCATTGTATTTAAATTTTGTAGTTGAATGACTGTGGTTCCCACTAT
AATATCTAGCATGCAGAGAAGAGCAATCACAGAGCTCTTCAAGGATGCAGCTGCTGCCCTCACAAATCTA
TTTCACAATGTGCTGGTCAAAGGTATATCTTCTGTACTCTCCCAGCTGGGATGAGTAGGACTAAAGTGAC
GAATTCACTCCACCATCCCAATCTCCATAAGCCTTTGGATCCCTTCCTCTACATTAAACCAAGGGAGATC
AGGCATTTCCAGCTCACTCACAGTGGGCCACCTTTTGATCTATATTTCAGCTAACCAAGCAAATAAACTA
TTAGAACCTTTTTTAACTCTCCAAGCTGCAACATTAAATGCAGAATTCCTGCTTAGTGGGCCCAAATCAA
TCAATTCAGCCTGATCCAACTTTATGTTCCTTCTACCATTAGCCCACACCCTTAATATCCATTCCCATGC
CTGTTCTCCAGATTTCTGCTTATATAAATTAGAAAACTCAAGCAGTTCTTTTGGAGTGTAGCGCACCTCC
TTGTGGGTCACATTCTGAACCTCATCTCTAAGGGGCCTGCCGGGACTTTAGTCTAGTTCTATAACTATAA
GCAAACAGGGGTATTGAGGGTGGGTCCTTAGGAGAATCAACATCGTCTTTCCTGGCAACTGCCTCAAGGG
AGGTCATCGCTGATGCCTTAGGCAGTGCAGGGTTAAACTCCTCAGACAAAGGTGAAAAGCCTGATGGCAG
CGCAGGTGGAGGAGGGGATGTTGCCTCCCCTCTGTTGCCTGTTTCCTCTGGTAAAAAAGATTCATCAGAA
TTTAGAAGCTCAGTGCCCCCAGCCTTATCAGGGTCCTCCCGCATGGCCCCATTCCAAGTTGCAGGGTACC
ATTCTTTTTCAATCAATGCTGTCACTTTAACAGTAAACACCTGGCAAGGCTGTGCACGTACCTTTCGTTG
CAGGTCAGCCACTCACATGATAAGAGCTTGTGTCTGATTTTCCGCAATTTCAGCTCTTTCTCTACAGGAG
ATAAGACTCGAACCCAGGGCAATCTTAGAAGATTTGAGGCTCAGAATGTGGTTCTGGAGCTGGGAGATAG
AATCCCTGAGTTCATCATTTTTTTGTTTTCATCACTTTGATTAGTGAACTTAGGAGCAACCAACTAGCTT
CATTATATTCCTTGGTTCTCCACATATGGTCAAAGGTATTAGGTATAAAGTCACTAAACTCCTTGCCTCT
CATGAGCAGTGAATCAGGAGTATCAGATGCATTTATTTTGCACAACTCTCTACACAGTTCACAGCAAGGA
CTATCAGTGTTCTCCACACTATTAGAAGTAGAGTCCCTAGCATTTTGGCGTCTAATCATATTTAGCAGCC
AACTCCAGAAACCCCAAAACCATCTAAAGAAATCCATCCTTAAAATTCTGTTCCTCTAGAACCACTCCTG
GTACCAAAATCTGTATTAGTCAGGATTCTCTAGAGGGACAGGACTCACAGGTGAGATGTATATATAAAAG
GCAGTTTATTAAGGAGAATTGACTCACACAATCACAAGGTGAAGTCCCACAATAGTCTGCAAGCTGAGGA
GCAAGGAAGCCAGTCCAAGTCCCAAAACCTCAAAACTAGGGAAGCCGACAGTGCGGCCTTCAGTCTGGCT
GACAGCCTGAGGGCCCCTGGCAAACCACTGGTGTAGGTTTAAGAGTTCAAAAGCTGAAGAACTTGTAGTC
CAATGTTCGAGGCCAGGAAGCATCCAGCACAGGAGAAAGATGGAAGCCGGAAGACTTAGCCAGTCTAGTC
CTTCCATGTTCCTCTGCCTGTTTTTGTCCTAGCCATGCTGGCAGCTGATTAGATGGTGCCCACCCAGATT
GAGGATGGGTCTCCATCTTCCAGTCCACTGACTCAAATGTTAATCTCCTTTGACAACACCCTCACAGACT
CACTCAGGAACAATACTTTGCATCCTTCAATTCAATCACATTGACACTCAGTATTAACCATCACCCTAGG
CTTTAGGGATATAGGGAAAAACATGACTCATTGCTGTTATCTGAGAGTACATAATCTATTGGAAGAAAGG
AAAACAGTTACATGTAAGGCTTATATCAGTATAAATTAGATAACTGCCAAGTGAGAGAGGTAGAGGTAGC
AAGTGCTGTCTGTGGGTGCATGTTAACTCAGTCTTAATCTTGGAAGAAGTGGCAGTGTGGAATGGTACAT
GGAGAAGCAGAAGGGACAATTACTGTGAGCAGATGAATGGCTCACTACAGGGGCATGGGAAGAAGATGCA
AGAGCAGTGGAATCTTTAATTGACGAACCTGGTACCAAGCTGCCAAGTCTTAGTCTCAGGACTGGCACCG
TGCACTTGGCCATTGAAAAGACTTTGGAACCTGTGGAGTGAAGAGTTGTAGGAATTTTCAAAGCCTCAGT
GTAGGAACAATGTGAGAATCAACCAGGGCATGGTACTCCACACTGTGTTCAGATCCACTGGTGTTAGGGG
AGTCCCAGAGAGGCCTCTTAGAGGGTTGAGGAGGATGGGATCAGGCATAGCAGAGACTAGGGACACGAGG
CTCTGCGGCCAGACTGCAGGTCTGCTACCAACTACAGTGTGATTTTGCCTAGTCACATAATCTCTGTGGG
CCTCAGTTTTTTGTTTTTGTTTTTTTCTATTACAACAGTACCTTTCTCGTGGAGTTGTAGTGATTAGAT
ATCTAGTACCAAGACTATGCTTGTTAGCACTGAGTAAGAACTCAATGAAGGTTAGCTTTCATTGGTACTA
TATTACTATTGTTAGTGTTGGTGGTGGAGCTGAATCGCCTAACCTATGAGGTTGGTGCTGAAATGAAGAA
AAGAATAACAGTGTTTTAAGAAGTTTGGTCACTAGAAGTGGAGCTTAGTAATTAAAGAAAAAGAGTGAAC
ACTTTTACCTTCTTGTGGAAGTTAGTAAGTCTACAAAATGTTAATTCTGCATTTGAATGATCATTTGGGA
GACTCTTATTGTCCTATTTGCACTGAAAAAGTCACTGAATCATTATTTTAGAACTGGAATAACGCCTGAG
ATCTAGGCCAGCACTTTGCAAGTTGTGCTCTATGGGACTTTTCATGGAAGTGGCTGAGGAGTTGCCTTGA
AGGAAGGCAGAGGGAGTGGGTCTTGGGACACCCTTCCAGTTATAAAACAGGACGTTGATTCTGTTTTGTA

FIGURE 1, page 81 of 93

GTTGCAGCATCACATATAATTTCATTTATTAAGAGGATCCCACTTCTAAAAATAAGTTGAAAACCAGTGA
TTTAATCCAGCCTCTCTGTTTGCATATGAGGAAATGGAATTCCGGAAAGGTTAGGTGATTTGTCCAAGGT
TGCAGACTAGACTATTTATTAATAGAGTAGGGTCAGGAACAAAAGCCTGCTCCTTGCTGGTCCAGCGCCT
GTTACTAGTTACATAATGAATGCTACCTATTGCTGCACAGTGCCAAATCATTGCACTTTTCAGATTTTAC
TCTAATCAAAAGAAAAAAATTAAAGTGCACTTCCAAATCAGTACTTATATGCAAGAGCTTCAAGAAACAA
ACTAGTATTTAACTTGGTGGTTACATATTGACTGTATTTTCATTGAGTGAGGTTAGAAGAGATTGAGAAG
CGTGAAATGAAGTTACAAAGTAGAAACTATATGGTGAACTCAAGGCAAAGATTGTCCATAGTAAAAGAAG
ACAAAATAAGAATGAAAGAGACAAAAGAATTGCCAATGAGTTGTAATCTTAAAAGAAAGATATATTTAAT
AAAATAGGATTGATTGTTTTGAATGTGGGCTGAGAAGTCCTGCCATCTTCCATTGACTCTGCTCACAGGC
CTTGTTTGTGAACTGGCTTCCATGGATAGCATTACTCTCCTGACAGCTGCAGCTCCAAATTCAGCATGAA
AAGGCTGGCAATTCTAAGAGGAAGGGAGTGTTTAGGCCACTTTTAATTCTACTTTGTCATTGCAAGTTTC
TTGCATTGTTTGGCATTTGTTGGTCTTCCTTACTGGATTTCAAAACTAGAACACTTTTTCCTAGCCTTGG
AACCAACCACGAAAATAACCACCTCTTACCCTCATGAAGAACACTTTAAATTTTTCTCTTTTAAAAATGA
AGTCTGGAATATCTCCAAACATCTTGTCACTCACGCCTTCATTTAAATGTCACCCTCTCAACCACAAGGA
AACTAAAATTGCCCCCTACTTGCTACTCCCTGTTTTATTTTCTAGTAGAACATACTACAGTTGGAGATCA
TCTCATCCATGTCTTTTATTCTTGTCTCTTATTTGCCTCTGCTTGACTGTAAGCTCATGGAAAGTAAGGG
ACCTTCACCAACTAGCAAAGTGCTTAGGACCTAGTAAGAACCTGGTCAATTCTAACTGAGTGAATGACTG
AATTCCTGTGAGAAGTCAACATGAAAATTCCTAGGTCATTAGTTTAGTTATTGGAACTCCAACACTGTAT
TGGAAAAGTGTCATGGAAAGGATAGTTAGTGGATTAAGGTTTTTATAAGAGGAAGAGGGAAAGAAAGGC
ATTGTCTTTACTTCAGGCATTTCAATGGCCATGATGGAGCCTAAATATTGTATGTTGCATTTTGTTTTGG
TTTTGTGTGCACAAGAGCTTTGACAGTGGAATGAACGGGTTAAGAAATGTGAGTTTTCTTTTCGTCCTGC
TATAGAGACTTAAGGAATTGCCCCGTGTGAGTTCCTTGAGGGCAGAGAAAAATACAAATCCATGAATACC
TGAAAGCCCTGATTTGGCCCCTAAGCAATCTATGCATGTAACAACATTGCATTTGTACCCTGTACATTTA
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AATGTTACTGTTGTGTGGGGTTTTTTCTTTGCATTTTTAAAGTTAACCTGGATTTTTCTCTCACTCTTT
ATGCATGTATTTCCTAATCTCCCTATAAACTATTTGTATTTTTTTGGATTCCTCACAGTCTATTTAGCCT
GTGGACTGTCAACAGATGTTACATCATTCAGTCATTTAATAGATGCTTATTTGCTAGACATGGCCAGGAG
GACCTGGAAAGTCCTCATTTTTCCCATCTGTTCTTACCATTCTGAAATGTATCATGCTCTTCAGTGCTCC
ACAGATCTAGATGATATCAAATTATTAAATGGAAAAAGCAAGACCCATCTCCTTGGGTTATTGTGGATAA
GGGGGAAATTGTGTAGGAAGTGTCTATTGCAGTTCATGGACCATTGTAGGCCCTTAGTCAACAACAGCTA
TCATCATCACTGATGAGAATCTCTGGCTTAAACGGAGTAGGTTCATGCCTTTTTTCAGTGTAATGAAGTG
TTTTAGTTTAAAGGCCTTTAGCAAGGCTTACAATAAAAAAAAGTGGGGACTCCAGGGTAACACCAACAAT
AGAGACGACCATGGCTGTTATCCTGAGACTATTAATTATGCCACGTAATTAGATTTAGAGAAAACTTAGA
GCAACATTTATCTTGTGGATAATAATTGATTGTGATTGGGACTTACCGTTGAGAGACCCTGATGAAAACT
CTATGGTGAATTGCTGTGGAGTCACATGGGTTCATGCATCATTCATCAGTGGGCCCTGGTTTTAGCCTCA
TAACCCCTGAGAATCCACCTCTATCAGAAAACCACCCTTTCAGTGAAAGTTCCTCAAGGCTCAGAAAAAT
TCATATGTCAAAGCTTTATATGTAAAAACCTATACTCTCTAATAAATGTTTGGTTTGGCCTTCACATTCA
ATTTAATAATTATTTCTACCTCTTTTCTAAACCGCTCTTAACCACAGTTCTATATATTTAATTCTGAAGA
GCCTCATGCACCTCCCTCCCTGGTAACTTTATCTACTTCTCTCCCTGGAGAACCAGCCAGACCATGATTC
CAGCCCTCTGTCCTCTCTTCAACCGTAGGTCCTCTTTTTCTCTCCTGACTCCTCAAACCTTCTCCAGTTA
CCCGGATGCCTTCTGTGTGCTGCTGGCTTCTGCATCACTGTTCACAGGGCCACTTGTTCCCCTGGAAATG
TCTTATGCTCTTGAAATGCTATAGCCTTGTTCACCTGTTCATCCAAAACTGATCCTCAGACAACATTTCT
CTTTCAATTGGTGGAATAATAAAGAGGAATATGGGTCAAAATTCATAGACATTTAAATACCCAAGGTGCA
AAGTTAAGAGAAAACAAGATAGGAGAAAGAATTATGGCAACATCTCTAAAATGTGTACTTTAGTGTTTAG
CAAAAAAGGGACTATGGAATGTCAAACAGGAACATATATGTTAAACATAAACATGAAGCAGTGCCAGCTG
CTGTCTGCCATATAGTCATGCTTTGTTAATGTGGCACATCTTGCCATGATGGTGCCCTCATGAAACGAAG
GATGCTGAAGCAGATGCCATTCTGTTTGCTTTGATCAGAAGCCACTCTCTGGTCAAGGAAGTATTTGTTT
CATGCTTAATTATAACAAGTTCTCATCACAAAGATTATTTTCTTTCTCCAGATCTGGATTGTTTGCACTC

FIGURE 1, page 85 of 93

ACTTTATATTATTAGACAATTACTCAGATTGTTTATGTTTTTATGTTTAGAAATAAGACAGTGATTCAGA
GAGTCCCTGTATTTAGATGAAAGAACATTTTTAAACATATTGACTGTAAACACTGAAAATCATTAATTC
TCAACAGTTGAAGGTTTCTGACAGGAACGGCCCTTGGAAATTGTAAATGGGCACATTGTCAGGTATGCCC
ATTGTTGTCACATTGGAGAAGATTGGATTCTGTTCTCTCTGGAGTCCTTTGTAATGCCAAGCTTCCTCTC
CAGGGAGCTGGCTTATTGTCATTATTTGAGATAAATGGCACTTCATAGTATTAAGTGGTTCATTGTCTC
TTCTCTGGCTGACTGTATTCTGTAGGCAGCCACTCAACTTTGGAGCCTTTCTCTGCTACCAACTTTTGGT
GTTGCCTTAAGCAAGCCTCATGGCTCCTGTTAGTTTCCTGACAACATGGTATAGCATGGACTTTGTCATC
AGAGAGGACTGAATTCAGGAGAAGCAACTCTGCCACTTCCTTGGCGGAAGGGGGATGACTGATGTCCTTT
GATAAGCTGCTTCCCTGAGCCTAATAAAAAAATAGAAATAATGATACTTAAACTCATGGAATTGTTGTGA
CAATTGAAAGAATGACCAGTTAGTAAAGCATCTTGCACCATGACTAGCACACAGTAGATGCACATGAGTG
TTACTAAGCTTTAGTTATGCCCTCCAAATACAAAGCCTTAGTTTTGTCACTATGAAAGAAATTACTCTGT
TCTTCTTAGCAGGTAATAAATAAATCCCTGCCTGGAAATTCTGCAGGAGAATTTCACCCCTGCGCTTTCA
GGTTAAAAGATTGCATTCCCATGATGAAGATGTTCTGTGAATAGAATCATCTCAAGTCCCAAATGGTGTG
GATTTGCTCCTGCATCTTGTTGCAGAGATTCTCTTGGAGCTTCTGAGAACTGGGGAAACCAACAAAATGC
CTGTAGCCTGGGGAAAATGTAGGGAGTTTTAGCATGAATTTGTGGGAGGTGAGAAAAGGCAGCAGGTGTC
GAAAGACGGGAAATCCTTGCACTGTTCTAGATGTTAGGAGCCATTTTCCATTCACATTCAGCACCTCAGG
AGGAGAAGCTGCCTATCACTTTGTGTCCTCAAGAGAACCAACAAAGGAGAATGCCATCTCCCAGATACTC
AATTTGATTACCATTTTATCCTACCTTCTCTAGGGTCCAGACATTATGTAAATTGGCATTAAGTTTGAAT
AATGTATGGACCCAGTTTAAAAGGAAAAAATGCTTTGGGAGGCTGAGGCAGGTGCATTGCCTGAGGTCAG
GAGTTCCAGACCAGCCTGGCCAACACAGTGAAACCCCATCTCTACTAAAAATACAAAAAGTTAGCTGGGC
ACGGTGGCGGGCACCTGTAATCCCAGCTACTCAGGAGGCTAATGCAGGAGAATCACTTGAACCTGGGAGG
CAGAGGTTGCAGTGAGCCAAGATCGTGCCATTGCACTCCAGCCTGGGTGATGAGAGCAAAACTCCATCTC
AAAAAATTTTTAAAACAAAAGGAAAAAATGCTCCCCTGATTCCCGCAGTGCTGACTTAAAATGTTCTTAG
TATGCCAATGTTGCTTAAATATGAATGACTGTAGCTTCTACTTAAATTGGCAACCGCACCAAATATAAAC
TGCAAATGTTTATAGCTCTTATGGAAGTATAAAAGCAAAACAAATTCTTAAATTAAATACAAACTAAGAG
GGAAACTGATAATAACAATGTTTTGTGTAATTAAGTTGCTGTTTGCAACATGCCTGGGGCAGACTCCTGG
CCTCTTTGCATCTGACATGAGAGGCTACCAAGGATGTGGCCACAACTGGGCTCTCCCAGCACTTGCTTGC
GCTCAGAACTGTGCCAAAACCTTTGCTCGCCCAGTGTTCTGCAACGTCCATCATTTGGATTTGGCAGGAA
CACATCATTTATGCATTTTGTTTGCTTCTGTATTTAGTTGAGATACTTAAATATAACTGCTAGATTCTA
AGGCATTCATAAGCATCTGTGAAAAATGTGTTACTTAGGAAACAGTTCAGGGTTCCATGGATTATCTAGA
TTGGTGAGTCTTAAGACTGACCACACAATTCATCTGGGGGTGTGGAGGAGGGGAGCTTTGAGAAAAATCT
CTGTATGAGCACCCACACCCAGAGATTCCTATGCAATTATCCCAGAGTGGTGCCTTAATATCAACATTTG
TTTAAAACCATCCCCCAAGACTAAAATTTGTGACCGGGATTTAGAACCATTGACTTAATTGATGCAGAAC
ACTCTGATATTAATGTCTTCATGTCTTTTGGAATGTCATTAAGACAAAAGCATAAAATTTTAAAATTCTT
AAAGACAATTTAAAGACCTATGAGATCCATCTTTAATTCTCAGGAGCGTGTGGAACCTAGTTTGAAAAC
TACTGGCATCGACAATTGAATTTCCACTAAAATAAAATAGCTCTCTAGTATATTACAAAACTACCCATTC
TGCAAACTGCAGGGGGAGCTACTGATCATGCTTGGAACTGTGCCAGGCACTGCCTGCGTAAAAATGAGTAA
GGTCCACTTCCTCCATGGACTGGGTTGGGTAGGAGGCAAAGATAATTAACCAATTATTTTAATATTATGA
GTTCAGGGTTGTAATGAAAGTAAGTATTGAGTGCTGCAGAGACCCAGCAAAGGAGTCCTTAGCTGAGAAC
TGATCCTTTGCTGAGTGACGAGGACATTATTGAACCGCCAGGCTTGATGGCATGTTGCATGGTAACAGAC
CAGTACACCAAACAGCAGGAGCTGTAGCAGAGAAAGAGTTTAATAATTGTGTGGCAGCCAAATAAGGAGA
CAGAAGGAAACCTTAAATCCACCTCTTGAAAAAGTCTGGGACTAGGCTTTTTAAGAGAATTCTGGCAAGA
AGGAGGCTGAGGAGCTGGGGGTAACTGATTGGTTAGGACATAGGAGAGGAGACAATAAGGATATAGAAAC
TCCATTCTTGCACTGGGTCAGTTCCTCGGAGGGGGTCCTCACTCTGGCTGGCAGCAGTGAACCCATTGGA
ATGCAGGATCTGAAAAATATCTCAAAATGGCAAACTTGAGGGGTTTTTTTAGCATCAAAGATGTTATCT
ATAGAAGTTAGGACATTGTGACAGGGGCTACGTGACTTTGAAGTGTTAAGTGGCTGTCAGAAAGTGAGCT
ATTGCAGCGGTCCCCAACCTTTTTGGTACCAGGGACCAGCTTCATGAAAGAAAATTTTTCCACAGATGGG
GTGGTGTAGGGTGGGGTGGGGGATAGCTTCGGGATGAAACTGATCCACCTCAGATCATCAGGCATTAGTT
AGATTCTCATGAGGGGCACACAGCCCAGATCCCTCACATGGGCAGTTCACAGTAGGGTTCACAGCCCTAT
GAGGTTCTAATGCCACTGCTGATCTGACAGGTGGCAGAGCTCAGGCAGTAATGCTTCCTTGCCCACCACT
CACCTCTTGCTGTGTGGCTCAGTTCCTGACAGATTACGGACTGGTACCAGTTTGCAACCCAGGCAGCTGG
GGACCTCTGGGCTGTAGGGTAGGCTGGTTAATGCTTAGCTGTGTTTCTATTCAAAGCTTATGCTTTTGTT
TAAAACCTAGTAATTTGGTTTTGTTAATTTTATGAAGATGATTTCAAGGATGAGTAGGATTAGCTGGAGT
CAGAAGGACACAAGGGAATTTCTGGCAACAACATTAAACTACCAGTGAATGTCTCATCAAGTCACTGGAC
CTCTAATTCTAAGCAGTACTGTCAACCTTATAGGTTATGATGTATAAGATAGTGTTGTGATGTATAAGAT
AGTGCAAAAACCTAAGTTAATATCACCATTTCTGTAGTACTCTCTATTTCAAAGGAAAAAATCTTCAGCA
GTCTAATATCCTACCAAAATTTTGAAGTCAAGACCTCCCTACACTAATCAAAGAACTAGAGGTGCAATCA
GGCCATATATTTGGAAAGGCCATAGGTGCCCTCCCTCTGTCCTTGTTCCCAGCATACTAAACTATAGTCT
AAAAGACTTTAAAACTTGAACTGAAGAAAACCTTAAGGAAACAACAACAAAATTCCATTTATTTCCTGAG
CCCAAAAGTAGAATAATTGTTTTTTAATGAATTTTTCTTTCCCTGTAAGACATACTATGAATTGTTCAAT
GGGTATTCAAAGCATATGTAATAGAATATGTATGCTTTCCTGAAAAATTGAAATGGAACATCAAACTGTT
CTGTAAAGTTTTGAGTCTAGACCAAACTCACAGCACTTAGCCAGAATATGTACATCTGCATCTGCCACTC
ATGGCCCCATCGCTCCCTCCAACTGCTTCTCTTGGGCTGAAGGATGGAAAAGCAAACTCCCTGCGTTGAG
TTCCATCTTGCCCTGCATGGCCTCCCCCATGGGGTCATTGAGCTCCCCACCAGCTTCCACCTCTTCCAGC
ACTTTCCGCCAGAGGGCCCGTGGCTGCTTTTGCAGACTGAAATTGATTGTGGTTGATTCAGCTCCATTTC
CTCTGAGTTTTTACTTTAGATGTGCTTTTTAGGTTGCATTTTTCTTCTGGCATATAAGAAAGACAGCAAC
ATTCCATGGAACAGAGTGATGTCTGTGGCTTTGTCAACCGTTGTTTGTTAGCTTGATCACCATTTATTGA
GTGTTTACTACTTTCCAGGCATTGTGCTAAGTGGTAGAAATACAAAGTTGCCTTTACTTGATTCATCTGT
AAAATAGAGAGAGTAGTAGTTCCTACAGTGTGGTTTATGTGAGGCATAGGGACTGCTCCCTGAAACCTAG
GGACAACTCCCTAGCAGCGACCCAGTGCTCATATCAATAGTGGTAACAATTAGGAAGGCAGCTCCTACCT
CAAAGACCTCATGATCTGATGGTAAAGACAGATATAACAAGAAAATTATTCTTTTTAAATATAAAATTGT
GATATAAAAATAGTTTTCACTAAATTGGATTTTTATGAAATTTACAGAAACAAAATAATAAATTAAGGAA

ATATAAAACCACCTGACATTAGCCAACCATGTTGATGTTCTGATTATGTTACTGCAAAGGAGTGTAGGGT
TAAGAACGAGGGACTTTGATTCCAAGATCAAATCCCTTTCTGCTATTTCTTAGCTGTCTGACTTTGGGCA
AGTTGCTTAAACCCTTTGTGCTTCTGTGTGCTTGCCCATGAGATGGAGATTATAATAGCGTCTACCTCAT
AGGGCTATTTTTAATACAAGTTAGCTCTTAGAACAATACCTACTTAAACTAACAATTTGTATTAGGTACT
GTTTTATTCTCCATCCGTACTGTGTATGCATATATTCATATTTATATTTACATATTCTAATTAGGATTAT
ATACATGTACTTTCTTTAAAAATAAGATTTAAATAACTATATAATCAGTCATGATGATACAACATGATT
TATTCAACAAATCTGATGCTGTTAAACACGTAAGTGATTTCTCTTTCAGGATTATAAATAACATTTGTTT
TGCATTTTTTTCATACATCTTTTGCTCACTTTTCATTGTTACTTTGTATATGTTGCTAGAAATTGATTTG
CTGGTGAAAAGGGTATAAACATTTTTAAGGCTCTTGCTACATATTGCCTGCTCTTCATACATATTGCCTA
CTGCCCCAGGAAACTATCAATTACACTTTTACCAAGAGTGTATGAAAGCATTCACATGAATGTAACCTTA
TCATGCAATGCGGGCCATGAGACAGAGGAGAGTTATGGAGGGTAGACGGCTTCCCCGCTGCTCAGCCACT
GCCCTCTCCTCTAAAAGAGCCACAGTCAGGAATTTCTACATAGATCCTATTATAAACATCTCCTTTTGAA
ACAAATTATCTTCTCTCAGAGCATTTTCTTCATTTTAGTATCTATATAGGTCCTTGTTATGTTCATTTTA
AGTTTTGTGACCTGCACTGACACAATGCTGATGAACTGCTTATTCCAGGCAGTCTGAGTTCTCAAAGCAT
TTGCATTTTATGTCTTATCCTCTGTTTTGGGCTCTTTGCCACTGATTTTTTTTTAAGTGATATTTTAAGA
AAGAGGAGGGTTGATTTGTTGTGAGTGTATCTCTCTTTAAAAACTTTTCTAGGGAAGGACAACCTCTTCC
AAAGACTTTGTTTGCTTTGTGTGATTGGCATGTCCTTCCCTGGTCAGTAATGAGCTTGAAGGAAGCTACT
GGACACGGGACTGAACATGGGGTTTTGCTATCACTCTAGCTGTGCCTTTCTCTAGTGATCAAGGAGATGT
TGGTTCAGAAAGTGCCCTGTCTAATCCCACTAAGGCCCGAAGGACCAAGTGCTGTCTACTCTCCAGATTC
TCTGCAACAGAAAGCAGATGCTTAGGCTTCATGGTCCAGGTTGGAACAGGTAGTTAGCTCTGAGGACAGT
TATGCATGAATGTCAGGAGGGGACTGGCAGGGGAACATTTATTTATTCTTTAAAATTGGAATCAACAGTT
ATGGATGAAACCCAGAATGCAAAATTCACTTTCATCTTGACACGCAACACATCTGTCCTTTCTCCTTGAA
TAGCAAGTATTAATCATTGAGTTAGACAATGTAACCTTCACATTCAGTGAAAGCCAAACACTCAGCACCT
TCTAGAAAAAATCTTAGTGCCATGCTTTCTTAGCATATTGCAAGTCCTCTGAGGATGATGTGTTGTTCAGC
TTTGAAGCTGATCTTTTGTACTTGCTTATGTAGCTCAGGCTAGTGATAACATGCCAGAGGCATTTCCAAC
TAAGAAAATTATTCACAGAAGCTTTAATTACAAATTTGTTAGCCCCACTTCCTGCTAAAATGGCCAGCCT
TGAAGAGTTTCGGAAATGTGAGCAGCCTTAAGGATGATAGAAATATTATGAAATAGTAATAAGTAATACC
CATACAGCAAACTCCTTTTTCTTTGGAGTATCCGTTCATCAGCCAGATTTCCCTCTCAACAGTCCAGGTG
TTGACGAAGATCATGAAATAATAGGAATGAAAGGGACTTCGATTTGTATTTTTAATAGCATTTTCCTCC
ACCAAATTACGAAAGTAATGCATGACCAAGGCAGAGAACTTGGAAAATACAGAAAAGCCACCAAGCAAAA
TAATCTCCCAAGAAATCATAATTTCACCACACAAAAGTAACCATTGTCAACATTTTGGTGAAAATCCTTA
ATTAAAGAGACTCTTAAAAGATGCCAGTTCGCTGCCACTTCTTCCTTTCTCCACACCATCCTGCACCCTG
TTTTGAAATGCAGAATTGTTTCTAAATCATTCCAGGAAAATTATTAGTTTTCTCAAATATCTCTGGAGGC
GAGTCTGTTGGCAGTCATTTCTAGTTTCTCACAAACCTTGAAGTTAGGAAATTATTTGTGTAGCTTTTGA
GCACTGGGCCAGAAGTGAGGGATGTTTGGGTTCTAGTTCCAGCTCTACCACTTATTTACCAACTGGCCGA
CCTCAGGCAAGTCCAGGCTAGCGGCCCCGCCTCAAGCCCCTCCAGATGCAGCATCTGCAACCCCACTTCC
TTCACTTCCTTTCGCCTCAGTTTCCCAACAATTTCCTAGTAATTGTACTGAATCATTGTTTTTCATTTTT
TACATTAAAATTTATTTATTTTATTTTATTTTTAAAGACTTTATTTTTTAGAACAGATTTAGATTTGCAG
CAAAACTGAGTGGCAAGTACAGAAAGTTCCCATATATTCCCTGCCCCCGCACATACACAGTCTCCCTCAC
TATCAGCATCCCCAACCAGAGAGGTACATTGGTTACAGCTGATGAATCTACATCGACACGTCATTATCAC
CCAAAGTGCATAGTTTGCATTGGCGTTGGGCATTTTAGGGCTTTTGACACATGTATGCACTATTGTAATA
TACAGAATAATTTCACTGCCCTAAAAATCCTCTGTGCTCCTCCTATTCATTCCTCCCTCCACCCCATTCC
TGGCAACTACTGATCTTTTTACTGTCTCCACAGTTTTGCCTTCTCCAGAATGTCATATACTTGGAATCAT
AAGGTTTGTAGCCTTTTCAGATTGGCTTCTTTCACTCAGTGATATGCATTTAAGGTTCTTCCATGTCTTT
TTATGGCTTGATAGCTCATTTCTTTTTATCATTGAATACTACTACTCCATTGTCTGGATTATACACACTT
TATTTATACATTCACCTACTGAAGGATGTGTTGGTTGCATCCAAGTTTTGGCAATTATGAATGAAGTTGC
TGTAAACACCCATGTGCAGGTAATTGTGTTGATATGCATTTTTAATGCTTTTGGATAAACACTCAGGAGC
ACAATTGCTGGATTGTATAGTATGTTTAGTTTTGAAGGAAACTGCCAAACCATCTTCCCAAGTGGCTGTA
CCATTTTCCATTTCCACCAACAATGAGTGAGAGTTCCTGTTGCTCCACATCCTCATCAGCATTTGGTGTT
GTCAATGTTCTGGATTTTGGCCATTCTAACAGGTGTATTGTGGTATCTCATTTTGTTTTAATTCGCATTT
TTTGGATAATATCACATGGAGCATCTTTTAATAAGCTTATTTGCCATCTGTGTGTCTTCTGTGGTGAGGT
GTCTGTTAAACTCTTTGGTCCATTTTTTTAATCAGGTTGTTTGCGTTCTTATCGTTGAGTTTTAAAAGCT
CTTTGTATATTTTGGATAACAGTCATTTAGCAGGTATGTCTTTTGCAAATATTTTCTCCCAGTCTGTGGC
TTGTCTTCTCATTCTCTGGAGATCAGTGGTTTTTACACTTTCTTCTGCTGAAGCCAAGTATTGTGGAAGA
AGCCATGGGGTCACCAGAGGATAGGTGCACAGGGTAGTGAGGGAAAGTTGGAGTGAATGGGCTTGGTGCC
CCCACCCCGCAACATTTCTCTTGCTTTAATCAGAGAAGTTTGACTTCATCCAGATTGCATATGAGGACTT
TACATGAGGTTCACCTTTTTATTTGTTTTAAAAGGGGTTTTTACTCTCAAAATGTTTTAAAGACCACTGA
ACTAGATGATCATCTTAAGGCCCTTTTAAGATTTATGATTCTGGAATTCTGTGGCTCTATTTTTCCAATG
TAATATAACCTTCCTCTCGTTAAGGAAAAATGAGATAAACCTGTTATAAACACTCATGTGACATTTTTTC
AATACAGTTTTCATCCACGTAGTGCTCACTTAGAATGATAGAAACAATACACCTAAAGAATATGCACCAT
TCACTTGCCCACTCATCTCTCAAAGAGAGGAACTTTCAACACTAGTTATCTTTTTAAAAATAATCAGAGA
GAATTCTCAGCCACTTCAATTCTAGCCCAGGAAAAAGAGGGAAAATACATTTGAAGGTTTCTGGCTCATG
TGATACATTTGCAAACCAGAACCAAGATGATATGACTCTCATTTATTAGTGACTATTGCAAAGCTTTGCA
GGCTATTAAGCAGGCTGTTCAATTTAGGGTGATATGGACATGTGCATATTGGCCAATTATATATGCTCAG
ATCGTATGTCATTTTTTTTTCTGCATTTTAGTCTAAGTGTCAGATAGGTGTTTCATGATGTTTTATAAACA
CTTCTGTTCACATTAACATTGTTCATTGATTTGGCAAGGAATGAAGGGGTGTCATTTTCATGATTTTATT
TGTATATTATGTATTCCACAGAGGATTTGAAATGCCTTACCAAATTTTATGTAATGTAAAGGGGTAAACC
AATATTTGACACATCATTATAAATTGAGGATAATCTGAAGAAAATAATAAATCCAGGAGACAGATTATCA
CACTGATATGGTTTGGCTCTGTGTCCCCACCCAAATTTCATCTTGAATTTTACTCACATAATTTCCATGT
GTTGTGGGAGGGACCCAGTGGGAGATCATTTGAATCATAGGAGTGGTTTCCTCCATGCTGTTCTCATTGT
AGTGAATAAGTCTCATGAGATCTGATGGTTTTATCAGGGGTTTCCACTTTTATATCTTCCTCATTTTTTC
TCTTGCCACCACCATGTAAGAAGTGCCTTTCGCCTCCCACCATGATTCTGAATTCTGAACCCTCCCCAGC

FIGURE 1, page 87 of 93

CATGTGGAACTGTAAATCCAATTAAACCTCTTTTTCTTCCCAGTCTTGGGTATGTCTTTATCAGCAGCAC
GAAAATGGACTAATACAGTAAATTGGTACAAGGAGTGGGGTGTTGCTGAAAAGATAGCCGAAAATGTGGA
AGCAATCTTGGAACTGGATATCAGGGAGAGGTTGGAGCAGTTTGGAGGGCTCAAAAAAGACAGGAAAATG
TGGGAAAGTTTGAAACTTCCTAGAGACTTGTTGAATGGCCTTGACAAGAATACTGATAGTGATATGAACA
ATAAAGTCCAGGCTGAGGTGGTCTCAGATGGGGATGAAGAAACTGTTGGGAAGTGGAGCAAAGGTGACTC
TTGTTATATCTTAGCAAAGAGACTGGTGGCATTTTACCCCTGCTGTAGAGATTTGTGGAATTTGAACTTG
AGAGAAATGATTTGGGGTACCTGGTAAAAGAAATTTCTAAGCAGCAAAACATTCAAAAGGTGACTTGGGT
GTTGTTAAAAGCATTCTGTTTTAAAAGAGAAACAGCATAAAAGTTCAGAAAATTTGCAGCCTGATGATGC
AGTAGGAAAGAAAAACCCATTTTTTTGAGGAGAAATTCAAGCTGGCTGCAGAAATTTGCATAAGTAACAA
GGAGCCAAATGTTAATCCCCAAGACAATGGGGAAAATGTCTCCAGAGCATGTCATAGGTCTTCATGGCAG
CCCCTCCCATCACAGACCCGGAAGCCTAGGAGGAAAAAAACAGTTTTGTGGGCCAGTCCCAGGGTCCCCA
TGCTGTGTGCAGCCTAGGAACTTGGTGCCCTGCATCTCAGCTGCTCCAGCTATTGCTAAAAGGGGCTGAG
GTACCACGGTTTCAGAGGTTGCAAGCCCCAAACCTTGGCAGCTTTCATGTGGTGTTGAGCCTGTGTGTAC
ACAGAAGTTAAGAATTGAGGTTTGGGAACCTCCACTTATATTTCAGAAGATACGTGGAAATGCCTGGATA
CCCAGGCAAACATTTGCTGCAGAGGTGGGGCCCTCATGGAGGGCCTCTGCTAGGGCAATGAGGAAGGGAA
ATGTGGGGTTGGAACCCCCACACAGAGTCCCCACTGGGGCACTGCCTAGTGGAGCTGTAAGAGGAGGACC
ACTGTCCTCCAGACCGCAGAATAGTAGATCCACTGACAGCTTGCACCATGTGCCTGGAAAAGCCACAGAC
ACTCAACGCCAGCCTGTGAAAGCAGTCAGGGTTGGAGGTGGTGGTGGCTATACCCTATAAAGCCACAGGG
GCAGAGCTGCCCAAGACTATGGGAACCTACCTCTTGCATCAGCATGACCTGGATGTGAGACATTCAGTCA
AAGGAGATATTTTGAAGCTTTAGAATTTGACTGCCCTGGTGGATTTTAGACTTGTGTGGGCCCTGTAACC
CCTTTGTTTTGGCCAATTTCTCCCATTTGGAGCTGCTGTATTTACCCAATGCCTAAACCCGCATTGTATC
TAAGAAGTAACTAGCTTGATTTTGATTTTACAGGCTCATAGGCAAAAGGGACTTGCCTTGTCTCAGATGA
GACTTTGGACTGTGGACTTTTGGTTAATTCTGAAATGAGTTAAGACTTTGGGCGACTGTTGGGAAGGCAT
GATTGCTTTTGAAATGTGAGGACATGAGATTTGGAGAGGCCAGGGGTGGAATGTTATGGTTTGGCTCTGT
GTCCCCACCCAAATCTCATCTTGAATTATACTCCCATAATTCCAAAGTGTTGTGAGAGGGACCTGGTGGG
AAACAATTTGAATCATGAGGCCAGTTTCCCCTATACTGTTCTTGTGGTAGTGAGTAAGTCTCACGAGATC
TCATGGTTTTATCAGGGTTTCCGCTTTTGCATCTTCCTCATTTTCTCTTGCTGCTGCCATGTAAGAAGTG
CCTTTCACAAGCATAAGGAAGAAGTATACTTGCTGGAGCAGCAGGCTGTCCTTCTTCTGACGATATGGAC
TGCAAGTGCCTATGTTTACTTTGACCAAGATGGCCTTTCTTTTCACAGAAAGCCAGGGTTCACCCCTTGA
ATTTCATAAGACCTCTCTTTGCAGTGGGTTAGATACTCTTTTATATTTTTATACTCTGTCAGGAAAACAT
TTTTTTTTCCATTTAAAAATCAATCTTTTGGTTGCTTCCAAGATGGCTGAATAGGAACAGCTCTGGTCTG
TAGCTCCCAGCGAGATCGAAGCAGAAGGCAGGTGATTTCTGCATTTCCAACTGAGGCACCTGGTTCATCT
CACTGGGACTGGTTGGACAGTGGGTGCAGCCCACGGAGGGTGAGCCGAACTGGGGCAGGGTGTCACCTCA
CCCACAAAGTGCAAGGGGTCAAGGGATTTCCCTTTCCTAGCCAAGGGAAGCCGTGACAGACTGTAGCTGG
AGAAACAGTACACTCCTGACAAAATACTGCACTTTTCCCCACAGTCTTGACAACTGGAAGACCAGGAGAT
ACCCTCCCTTGCCTGGCTCAGTGGGTCACACGCCCATGGAGACTTGCTCACTGCTAGCGCAGCAGTCTGA
GATCAACCTGCAATGCTGCTGCTTGATGCGGGGAGGGGCGTCTGCCATTGATGAAGCTTGAGTAGCTCAC
AGCGTAAACAAAGCAGCAGGGAAGCTTGAACTGGGCAGAGCCCACCTCAGCTCAGCAAGGCCTACTGCCT
CTCTAGATTCCACCTCTGGGGGCAGCACATAGCAGAACAAAAGGCAGCAGACAGCTTCCGCAGACTTAAA
CATCCCTGTCTGACACCTCTGAAGAGGGCAGTGGTTCTCTCAGCACAGTGTTCAAGCTCCAAGAACCAAG
AGACCGCCACCTCAAGCAGGTCCCTGACCCCCATGTAGCCTGACTGGGAGACACCTCCCAGTAGGGGCCG
ACAGACACTTCAAACAGGCAGGTGCCCTCTGGGACGAAGCTTCCAGAGGAAGGATCAGGCAGCAATATTT
GTTGTTCTGCAGCCTCCGCTGGTGATACCCAGGCAAACAGGGTCTGGGGTGGACCTCCAGCAAACTCCAA
CAGGCCTGCAGCTGAGGGGCCTGACGGTTAGAAGGAAAACTAACAAACAGAAAGGAATAGCATCAACATC
AACAAAAAGGACATCCACACCAAAACCCCATCTGTAGGTCATCAACATCAAAGACCAAAGGTAGATAAAA
CCACAAAGATGGGGAGAAACCAGAGCAGAAAAGTGGAAAATTCCAAAAACCAGAGCGCCTCTTCTGCTCC
AAAGGATTGCAGCTCCTCACCAGCAAGGGAACAAAACAGGATGGAGAATGAGTTTGATGAGTTGACAGAA
GTAGGCTTCAGAAGGTCGGTAATAACAAACTTCTCCAAGCTAAGGAACATGTTCTAACCCATCGCAAGG
AGGCTAAAAACCTTGAAAAAAGGTTAGATGAATGGCTAACTAGAATAAACAGTGTAGAGAAGAACTTAAA
TGACCTGATGGAGCTGAAAACCACAGCATGAGAACTTCGTGATGTATGCACAAGCTTCGATAGCTGATTT
GATCAAGTGGAAGAAAGGATATCAGTGATTGAAGATCAAATTAATGAAATAAAGTGAGAAGACAAGATGA
GAGAAAAGAAGAGTGAAAAGAAACGAACAAAGCCTCCAAGAAATATGGGACTATGTGAAACAAACAAATA
TATGTTTCATTGGTGTACTGGGAAGTGATGGGGAGAATGGAACCAAGTTAGAAAACACTCTTCAGGATAT
TATCCAGGACAACTTCCCCAACCTAGCAAGGCAGGCCAACATTCAAATTCAGGAAATACAGAGAACACTA
CAAAGATACTCCTCAAGAAGAGCAACCCCAAGACACATAATTTTCAGATTTAAAAAGTATGAAATGAAGG
AAAAAATGTTAAGGGCAGCCAGAGAGAAAAGTCGGGTTACCCACAAAGGGAAGCCCATCAGACTAATGGG
ATCTCTCAGCAGAAACCCTACAAGCCAGAAGAGAGTGGGGGCCAATATTCAACATTCTTAAAAATTCTTA
AAAAAAGAAGAATTTTCAACCCAGAATCTCATATCCAGCCAAACTAAGCTTCATAAGTGAAGGAGAAATA
AAATCCTTTACAGACAAGCAAATGCTGAGAGATTTTGTCACCACCAGGCCTGCCTTAGAAGAGCTCCTGA
AGGAAGCACTAAACATGGAAAGGAACAAACAGTACCAGCCACTGCAAAAACATTCCAAATTGTAAAGACC
ATCGACGCTATGAAGAAACTGCATCAATTAACGGGCAAAATAACCAGCTAACATCAGAATGACAGGATCA
AATTCAAACATAACAATATTAACCTTAAATGTAAATGGGCTAAATGCTCCAATTAAAAGACACAGACTGG
CAAATTGGATAAAGAGTCAAGACTGTGCTGTATTCAGGAGACCCATCTCACGTGCAAAAATGCACATAGG
CTCAAAATAAAGGGTCGAAGGAAAATCTACTGAGCAAATGGAAAGAAAAAAAAAAGCAGGGGTTGCAATC
CCAGTCTCTGATAAAACAGAATTTAAACCAACAAAGATCAAAAGAGACAAAGACAGCCACAACAAGAAGA
GCTAACTACCCTAAATATATATGCACCCAGTACAGGAGCACCCAGATTCATAAAGCAAGTCCTTAGAGAC
CTACGAAGAGACATAGACTCCCACACAATAATAATGGGAGACTGGGAGACACCCCCACAGTCAATATTAAA
CAGATCAACAAGACAGAAGGTTAACAAGGATATCCAGGACTTGAACTCAGCTCTAGACCAAGTGGACCCA
ATAGACATCTACAGAACTCTCCACCCCTAATCAACAGAATATACATTCTTCTCAGCACCACATTGCACTT
ATTTTAAAATTGACCACATAATTGGAAGTAAAACACTCCTCAGCAAATGTAAAAGAACAGAAGTCACAAC
AAACTGTCTCTCAGACCACAGTGCAATCAAATTAGAACTCAGGATTAAGAAACTGACTCAAATCCACACA
GCTACGTGGAAACTGAACAACCTGCTCCTGAATGACTACTGGGTAAATAACAAAATGAAGGCAGAAATAA

FIGURE 1, page 88 of 93

AGATGTTCTTTGAAACCAATGAGAACAAGGACACAATGTACCAGAATTTCTGGGACACATTTAAAGCAGT
GTGTAGAGGGAAATTTATAGCACTAAATGCCCACGAGAGAAAGCAGGAAAGATCTAAAATCGACACCCTA
ACATCACAATTGAAAGAACTAGAGAAGCAAGAGCAAACAAATTCAAAAGCAAGCAGAAGGCAAGAAATAA
CTGAGATCAGAGCAGAACTGAAGGAGACAGAGACACAAAAAGCCGTGCAAAAAATCAGTGAATCCAGGAG
CTGGTTTTTTGAAAAGATCAACAAAATTGATAGACCACTAGCAAGACTAATAAAGAAGAAAAGAGAGAAG
AATCAAATAGATGCAATAAAAATGATAAAGGGATATCACCACCGATCCCACAGAAATACAAACTACCAT
CAGAGAATACTATAAACTCCTCTACGCAAATAAACTGGAAAATCTAGAAGAAATGGATAAATTCCTGGAC
ACATACACCCTCCCAAGACTCAACCAGGAAGAAGTTGAATCTCTGAAGACACCAATAACAGGTACTGAAC
CAAGGTTTGGACCAACCAAAAATGTCCAGGACCAGATGGATTCACAGTTGAATTCTACCAGAGGTACAAA
GAGGAGCTGGTACCATTCCTTCAGAAACTATTCCAATCAATAGAAAAAGAGGGACTCCTCCCTAACTCAT
TTTATGAGGCCAGCATCATCCTGGTACCAAAACCTGGCAGAGACACAACAAAAAAAGAGAATTTTAGGCT
AATATCCCTGATGAACATCGATGTGAAAATCCTCAATAAAATACTGGCAAACCAAATCCAGCAGCACATC
AAAAAGCCTATCCACCAAAACCAAGTCAGCTTCATTCCTGGGATGCAAGACTGGTTCAACATACGCAAAT
AAATAAATGTAATCCATCACATAAACAGAACCAATGACAAAAACCACATGATTATCTCAATAGATGCAGA
AAAGGCCTTTGACAAAATTCAACAGCCTTTCTTGCTAAAAACTCTAAATAAATTAGGTATTGATGGAACG
TACCTCAAAATAATAAGAGCTATTTATGACAAACCCACAGCCAATATCATACTGAATGGGCAAAACCTGG
AAGCATTCCTTTTGAAAACCAGCACAAGATAAGAATGCCCTCTCTCACCACTCCTATTCAACATAGTGTT
GGAAGTTCTGGCTAGGGCAATCAGGCAAGAGAAAGAAATAAAGGGTATTCAGTTAGGAAAAGAGGAAGTC
AAATTGTCTCTGTTTGCAGATGACACGATTGTATATTTAGAAAACCCCATTGTCTCAGCCCAAAATCTCC
TTAAGCTGATAAGCAACTTCAGCAAAGTCTCAGGATACAAAATCAATGTGCAAAAATCACAGGCATTCCT
GTACACCAATAATAGACAAACAGAGAGCCAAATCATGAGTGAACTCCCATTCAGAATTACTACAAAGAGA
ATAAAATACCTAGGAATCCAACTTACAAGGGATGTGAAGGACCTCTTCAAGGAGAACTACAAACCACTGC
TCAACGAAATAAAAGAGGACACAAACAAATGGAAGAACATTCCATGCTCGTGGATAGGAATAATCAATAT
CACGAAAATGGTCATACTGCCCAAGGTAATTTATAGATTCAGTGCTATCCCCATCAAGCTACCATTGACT
TTCTTCACAGACTTGGAAAAAAACTACTTTAAAGCTCACATGGAACCAAAAAAGAGCCTGCATAGCCAAG
ACAATCCTAAGCAAAAAGAACAAAGCTGGAGGCATCACGCTACCTGACTTCAAACCATACTACAAGGCTA
CAGTAACTAAAACAGCATGGTACTGGTACCAAAATAGATATATAGACTAATGGAACAGAACAGAGGCCTC
AGAAATGACACCACACATCTGCAACCATCTGATCTTTGACAAACCTGACAAAAACAAGAAATGGGGAAAG
GATTCCCTATTTAATAAATGGTGCTAGGAAAACTGGCTAGCCATATGTAGAAAGCTGAAACTGGATCCCT
TCCTTACACTGTATACAAAAATTCGCTCAAGAAGGATTAAAGACTTAAATGTAAGACCTAACACCTAGAA
GAAAACCTACACAATACCATTCAGGACATAGGCATGGGCAAAGACTTTATGACTAAAACACCAAAAGCAA
TGGCATCAAAAGCCAAAATAGACAAATTGGATCTAATTAAACTAAAGAGCTTCTGCACAGCAAAGGAAAC
TATCATCAGAGTGAACAGGCAACCTACAGAGTGGGAGAAAATTTTTGCAATCCACCCATCTGACAAAGGG
CTAATATCTTTGTAGAATCTGCAAAGAACTTAAACAAATTTACAAGAAAAAAACAAACCCATCAAAAAAG
TTGGCAAAGGATATGAACACCTTTACACTGTTGGTGGGAGTGTAAATTAGTTCAACCATTGTGGAAGACA
GTGTGGTGATTCCTCAAGGATCTAGAACTAGAAATACCATTTGACCCAGTGATCTCATTAGTGGGTATAT
ACCCAAAGGATTATAAATCATGCTACTATAAAGACACATGCACACATATGTTTATTGCAGCACTATTCAC
AATACCAAAGACTTGGAACCAACCCAAATGTCCATCAACGATAGACTGGATAAAGAAAATGTGGCACATA
TACACCATGGAATACTATGCAGCCATAAAAAAGGATGAGTTCCTGTCCTTTGCAGGGACGTGGATGAAGC
TGGAAACCATCATTCTAAGCAAACTATCATGAGGACATAAAACCAAACACTGCATATTCTCACTCATAGG
TGGGAGTTGAACAATGAGAACACATGGACACAGCACAAGGAACATCACACACCGGGGCCTGTCAGGGGTT
GGGGGGCTGGGGGAGGGATAGCATTAGGAGAAATACCTAATGTAAATGATGAGTTGATGGGTGCAGCAAA
CCAACATGGCACATGTATACCTATGTAACAAACCTGCACGTTGTGCACCTGTACCCTAGAACTTAAAGTA
TAATAAAAAAAAAAAGAAAGAAAAGAAAAGAAAAAAAGAAGTGGCTTTTACCTCCCACCATGATTCTAAGG
CCTCTCAGCCATGTGGAACTGTAAGTCCAGTTAAACCTCTTTTTCTTCCCAGTCTCGAGTATGTCTTTAT
CAGCAGCGTGAAAATGAACTCATACACACACACAGAAGTATATCTTTACAGTTCCCAGGATGGACTGCAA
GTTTGGCTCTAAATTTCCTTTGCCTGGCCAAAACAAAAAGAACACATTTTATTATAAGGTTCACAGGCTT
TTAATTGAAAAAAAAAAAAAAACAGTTATTCAACATGAAAACTCTTTTTCAGACAAAGTTCTACAAAGTC
TATTTCTCACAAGTAGGACTTTGGCAAGGATTGTGCAACTGACAATTCAAAGTCATTTATTCCGTGGTGA
GAAACCGGAGTACAGATCTTTACCAGTTAGGGGATGATCCATGTGTTTTGATAATCACCTTGGTGGTGAT
CAGACTAAAGGTCTCCTATGAAAACCATTAACTTCACACTATAGCTGATAGGATGCACTGAAGCCCTTAC
CGCTGACTGCATGGATGAGAGCTAGGCCAGAGCATTGGCAGGCAGAGTTTATAACATGGGGCAGGAAGCA
TTGAAATTCTATTCCACCTCTTGGTGTATCAGGTCAGGAGTCAAATCTCCTATCTTCCTCTTCTGGATCG
CTTTCCTCCTGAAGTGTCTGGCATAGATGTCTAGGTATAGCTTGGCATGGTGGTGTGTGCCTATAGACCC
AGCTACTTGAGAGGCTGAGGTGGGAGGATTGCTTGAGCGCAGGAGTTTGAGGCTGCAGTGAGCCATGACC
ACACCACTGTACTCCACCCTGGGTGACAGAGCAAGACCCTGTCTCTCTTTCTAAAAAAACAAAACAAAAC
AAAACAAAACAAAAAGAAAAAAAGATGTCCAAGTGTGTTCTGGTTACTGCTGCTGACTGCTAAATTTAAC
AGCTAGAAAAAAAAAAGTTTGGACTCTATGGATCATAAATTTGGATAAGACACAGAGGGAATGGCTTGTCT
CATGTTCACAATGTCTAAAGTCTTAAATGGGGAGAGTCGTCAACCAGGGGTAATTTGAGAGTTATGGGCT
GGAACCACCTTGAGGCATCTTTATTCATAGGCTAGCAATTGATGTTGGCTGTTGGCTGGGACGTCAGCTG
GAGCTGTCAACTGGGAGACCTGTCTGATATCCCAGCATAGGACACTAGACCTCTCACAAAGTGGCGAGGG
CTCCAGAAGCAAGTGTCCCAGCTGACAAAAAAAAAAAGTTTCATAGCCTTCTACGACATGCACTTAGAAG
TGGTAATGTGTCACTTCCAGCCCTTTCTGTTGATTACAAGTGAGTCATGAGTCCACTCAGTTTCAAGGGA
GAGGGCCCAGATCCCATATCTCCATGGGAAGAGTGCCAAGAACACCTTGTAGAAAAGCTTGTGGATAGGA
GATATTGGTGTGGTCATCCTTGGAAAACACAATCTTCCACAGTGTGCAAGAGAGGCTTCCTGCTCTGCAT
TGTGGCTTAATTATTGTTGAAATACCAGGCAAGAAAAGGTAGGATCCAGGGAAACAAATGTATCCAGGAT
GTTTTGGTCTGCCTTTTCTAGGAAAAAAGGAAACCCTCAAAGCCTCTGAGACTAGGTCACCCCAGTGGGA
CTAGAAGTTCCACGTGGAACCTTCTGCAAACTCCTCTGCAATAGATGGACTGTGCATTTTCCAAATGTGT
CTTTACATCATCTCCTTTCTGACCTTGGGAAGATAGTAACTGACTGTGGAGTAGGAAATCCAGAACCCTG
ATTGTTTTAAAATATATTACAGATACAAGTAATGAAAAGAAGGCTCCTAAGGAAAATATAGATCCGTAAT
GGCTTTGTCCCAAAAGCTATTAGGCTATAATATTTTATTACAAAGGCTATATTTATTACAAAATGTATTT
AAATAAATACTTAATATTTATTTAAATAAATAATATTTATTTTATTATTAATAATTAATATTTAAATAAA

FIGURE 1, page 89 of 93

TATAATATTTCTTACAAAAATTAAAAACTGGGACTTTATATTTAAAGGTGAGACATTAAATTCTTTTTAA
AAAGTGCACATGTAAGATTTTTTTCTCAAGTCAACTGAACCAGTTCATCAGTTTCACTATGAATGTGTTG
ATGCACCAAGTATTTACTTTCTAGAACATCTAGTAGACGTCACTAAAAAATTATACCAAGTTGAAAAATG
TCACTGAATCAGAGGCATGTGGTTGGTTATGTAGTCATCTGTGCCAGCTGGGAATATAGCAATACCAAAT
GAACAGCACTGCCATGTTCCCTTGCTGGGTTCCAGCAAAAACACTCATCTTCACTGTCGTCTCTCTTTGA
GACCTCTTAGAGAGGACTTTGATGAGTGTATGGTCTTATACACACTAGTCTAACAATACACATTTGCTCA
AGGATTGGGTTACGAGCAGGCTCTTCACCTTTCAGGTGAACAATTACACATCAGGAGAAGGATGGAAGTT
TCCTATCTATGAACAAATATTTCCCAAAGCAATAATCTCTTTATTCAACTCACATAATGAGAAGTCAGTT
CCTCTGTGCCATAAAGCAATCTCTTTGAAGTCTTCAGTAATGTTGAGGGTTTTAATGTTGAGGGCTTTAT
CAAACTAAACATTCAAGTGTCTTAGGCTTTCCCCTTAGTTCTTTGAGCAAATTGGTTGCTATGAAGTATG
TTAGTGTTCCGAATGAATGGATAGCATGATGGGGGATGTCTAGGTGGTTCCAGAATTTAGATTGTGGTTT
CCATAACAAAGTGTGGCAGTATTGGCATTAGGGAAGAGAAATGACTTCTAAATAACTTCTCAAAGTTTAC
TAAAGCCTTAAGAATGTAGGAAATGGCCACAAAAGGAGGTATACAAAACATTCCTCTGTCTTTATTCCTC
TTTATACAAACGTATTCACTTTCCCATCAGCAAGTCATAAAATACTTCTCATCTTGCATTACAGTAGGAC
ACCTACTATAACAATAGGCTACAAAATGTATAATGGCTCAAACACCTAGCAGTTTATTTCTTATTTACTT
AACAATGCTGGGTCCACGAACATGTTGATATCATAACCCTCTTTTATGTGGTCACTCAGGGACTCAGGCT
GTTGAGGGCTCTGTCATCATGAATGGGTGGCTTCCAAGGTCATCCTAAGAGTTATCTCCATTCTAACCAG
TCCAGCCAGAAAGGCAGAACAGGCTTGGAGGAGCAAAGATATCCATGGATAGATCATCCTCTTAAAGTCA
TTGTAGCATTGTGATAGGGCTCTTTTCACAAAACAAGGATACAGTCCATGTTTTCAAGATTTTACATTTT
AGTAGCCACAATACAAAGAAGCTAAGATAGTCTTGTGATTTGTCATCATGGCTGTTAATGGAGAGTGTTT
TAAAAGCACTGATATCAGGGCTCCACCCTCAGCTTCCAATCATCAGGTTTGGATGGAACCTGACAGCTGC
ATCTTGTAAAACTCCACGGGAGATTCTGAGAGACAGCCAAGTTTGAGATTCACAAACCTTAAGAGAAAAA
ATCTCCTTGAATTGCCATAACAAACTACCAGTCTAATAAAACATACATATTCCTTTGACTACTCTTAAAT
GAAACAAATAGGTAATAATTTACCTGTACATATAATTAAAAATGTAATGTATTTTATAACCATCATATAA
AGGAGAAATTATATTAAACTATATTAAAATAAAATGATATATATTTCAATGCAGATGCCCAAGCTTGACT
AAAGTAGGAAACATAATAAAGTAATAAAATGCTTATATGTACTTATAATGAATGTTTGGCTATGAGAAGA
TGATCAGAGGCTTTTTGTCCAAGAAGTACAGGCATATGAAAAAGTAGAGCAAGAGATGGACACCAGACTG
AGAAAACTAAAAACTAACCAACCTATTTGTGTATGATAAAAGGAGAGAAAAAAAATTGATTAGTAAAAAT
ATGCTACCGTGTGGTCTGAATGTTTGTCCCTTCCAAAACTCATGTTGAAATTTAATCCCCCATGTGGCAG
TATTGAGAAGTGGGACCTTTAAGAGGTGATTGGTTCAAGAAGATTCTGCGCTCATGAGTGGTTGAAACCA
TTCACGGAATAACGGGTTAATGGATCAATGAGTTATCCCAGGAGTGGGACTGGTAGCTTTATAAGAGAAG
GAAGAGAGACCTGCGCTAGCACACTCAGCCTCCTTGCCATGTGAGCCATCTCGGGACCCCGCAGAGTCCC
CAGCAGAAAGAAGGCCCTCACCCAATGTGTCCCCTTGACCTAGGATTTCTCAACCTCCATAACTGTAGGA
AATGAATTCCTTTTCTTTGTAAATTATCCAGTTTCAGGTATTCTGTTATAAACAACAGAAAATGGGCTAA
AACACACGCCAAGAAAATTGAAAGACTGTGGAAGTGAAAGAAGAATAAAAAATGAAGTAATTTTGCAAAT
GAGTCTGGCTTTATTATAAGTGTATTGTCAAAGTGATTCCCTTTGTTATAAGATGAAAAAGAGCCAAAAT
GGATAGAAACATTTATCCTATCTTAATATCCCACTACATTCAAGGCAAATATTCAGTCAGTCTCTAGAAC
TTAACAAGGCCTTGGAGATGATATCCTTTGGATGAGCAATGGAGAAGACAAGATGGATTGGAAAAAGAAA
CAAACAAACAAAAAAACATGTAAGAGGCTATCAGGAAAACTCTGGAGACGATGTCAATGTAAAACAGATA
CAAACCTCAAAATAATTTTAATATGTACATTGCACAAAAATGGACTTCTTATCATGTTACAAATTTATTT
TAAAACATATAGGAGGCAACAACAATATTTCATTGATGTGTACTATTTTATAATTGTTGGCTCTAATTTT
ATTTAGTAGAGTCTTACATCTCCTCTCTACATATTTACATCCGGTTGTATTGTTTTTGTAGTACCTGTTC
AACTGCACTGAAATCATTTCAATTAAATGCATGGTTGAAAAGCTGACATAATACATTCAATTGCCAAATT
GCATAAAGTGAATAAGCTATTTAATAATTTGGAGAAAATATATTCCATTTAAACTTCCTTCTCTATAACC
AGTTCATACACTGGACCTTTTGGGCACAGCCATGTGAAAGCTTTTCAAAACTTTTCACTACTTTTTTTTG
AGACGGAGTCTCACTCTGTCACCCAGGCTAGAGTGCAGTGGTGCGATCTCGGCTCACTGCAACCTCCACC
TCCCAGGTCCAAGTGATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCACCTGACACCACAC
CTGACTAATTTTTGTAATTTTAGTAGAGACAGGATTTCACCATGTTGGCCAGGATGGTCTTGAACTCCTC
ATCTCAAGTGTTCCGCCTGCCTTGGCCTCCCAAAGTGGTGGGTTACAGGCATGAGTCATTGCACCCAGCC
ACTATAGATTTTTATTTGTAGTAGATTTAGTTCAGTAGGGCATTTGAGAGGCATAGGAACTGGAACAAAT
CCTTCATTGTTTGGGACTGCCTTGCACATTGTAGGACATCCAGTACAGTCCCTTCCACGAAGTGGCAGCA
GCAGCCTCGGGCTGTCCAAACACCCTGTTAGGGACAGTGCCACTCCCGGAACCACAGAAGAACCACAATC
ATAGGAGAAGCATACAACAAACATGGTGTTCATCGGACGGTCAGCTTCAGTGGCACTTTTGAGCAAGCAC
ACTATTTGGTTGTAGAATGAGTCCCTGGCAGGGCACCCGAAAGGCTGATGTGTGACTCATCCCTAGTACC
TCTGAGAATGCTGAAATCTCCTCCTTCTCCAAGCTGAGTGGCAGCTTTCTGGTCCAGACTACTTAAATTG
TGACTTGAGGAATTTTCTTCACTTTTTCCTTTGAGTCATTCTGTTTTTGATCAAGATGCGATAGAATGAA
GGATTCTTTCAGGGTCTGCTGTCACATCCTTCCTTTGGGAACAGATAGAAAATCTGGCCTGGCTTGAAGA
GTTTGTCCTCAAACATCTGGTAAGCCATAGGCATCAGCATCTCTTACTTCTCCAGAGACATTTAGATGTG
TCCCCCATCTCCATGGAGGCCCATGGCAAGGGGACCCCTAGTTGTACTAGAGCTTCCTTCTGGGCACAGC
CACACTGCACAGGCACTGCAGTGTACAGCACAGCTCCTCCAGCTTCCGGAAGACTCCATTATCTAGAAAA
GTGCTGAGAAATGGAGAAGGGGGTTCCTCTGGGGTGGAGATGGAAAGAGGAAAAGGAAGGGAGAATGTCC
AAGCAAAATGAGAGAAGGTGAGGGACAGCAGAATTGAGAGTGAGGGAGAGGGAGAGAGCAAGAGACTGGG
TTGAGATGTCTTGTACATGGGGGTGTCCTCGTGGCTTCACTCCCCTTTCGTTTGTACCACTCCGTTTCCC
CAGACTCTTCCTAAATATCCCCTTATTGGCTACAAGATCCAGATTGCCTAGAAGCTCAGATTTGCTGACA
GCACCTCAAGACTGGATAATGACATATAGATTTTTTCTTGTTTCCATCTTTGGGATTTGGAGCAATCTCC
AGAGCTGCAAAAGCCTACCTTGTTGCAATAATATTTTTGAGGGTCCACACTGTCTGCTCACTTGCTCTAT
GCTGCTGGGCACAGTGGTGTGGCCATCCAGGGTGGGAGAGACCACCTGGGATATGGAAATTACCAGCAGC
CCTGTTTTGCTCTTGCAGTGGTTGCCAAAGCACACGAAGCATTCTGGGAATCTGAATTTCTGTTGTTTCT
CCCAAATGGCCCCTGAAGGGCAACAGGCAGCACACATGGACCACATTTTGCCAGAAAAGTCCAGAAAGAA
GATGGCTGCTGTTGTCAACTATTGGCATTTCAACAGGACCTATTTTTATTTCTCAGTATATTTGCACAAC
TAGGAAGCATCTGCTGACAAGGATGAGATGATAAGCTGTATTGATGCCAAAACAGGACTAGAAAAACAGG
CTTGTTCTGCAAATGGCCTGCATCCTGAGAGTCCGTGTTAAGAACATTCTCTCTCTGCAGGCAATATCTG

CTCTTAAAACATTAACACTTGAAAGGAAGTAAGGCTTGGAATCCTTAGCATAGTTATGCACACACTAGGT
TCTCAGTAAGTGCATGCTGGATGAAGGAACCCACACGCACCTTAAGGAGGATGGAACATTGGCAGCCCAA
GAAAAAAGTCACTCCCCAGAGGCCGAGTGCCATGTCTTTGACCTCCATTGGCAAGGTCATGGTGAAATGC
TGTCTCTTGGGGTCGCTGAGGTCCCAGCACGGTGTGCCTTCACACCGTGCAAACAATAAGAAGAGAAGAG
ATGCACACATGTCACCTTTCCAGGCAGGGACATCCAAGCTGTTTGAGTCTCCATTCTGTGATTTCCTTGA
ACAAGAAAGGGATTATTGGTGAATGAGGCCAGCATCCTGGGTGGGAACAAAAAAGGAAATTGGTAGAAAG
TACATCATCCAAGTTGGTCTAACTCAGCCCTGTGGCTTGGGCGGGTTCCTAGGATATCCAGCCGGAGGCA
GAGGCTCTAGGGGATGTGAGGCTGCACTGGGTATGATGACACAGAGGACTGTGAGAGGCAGAGAAAAGGG
GAGAAGAGCTGAGGCCCTCCTAGCCCTAACCTCCCAGCTCACACCCTCTGCTATCTGCCACCTCCAGGCC
AACACCACGGCCATGGGAGGTTTGCCCATTTTTCTGATAGACACATTCTTTCTCTACCAACAGCCCACAT
GGAACATAAGTGAAGTAATTCAGCAGTTTCCTTCTTAATCTGCTGTCTCTCTGCTGCTTACTCATTCTGT
GCTGTTTGCTTTAGATCAAGGTGCCCCAGGGTACCAAAAGCTACATTATCCTATTCAACTGCATGGAAAC
CAAGATCCCGACCATTCTGGTTTGTTGTTATTGTTACGTTAGTTTTAAACCTTAGCCATTTTCCATTCTG
GGCAGTTACAACTCTGTTTACTATGAGTTCCTCTGTGTAGATGTTTCTCCCATACCCGACCTACAAACTG
CTACGTGAGCAGTAACTTGTCACCATGTTATCCGCATAAAGTCAGGGATTGATAAACTTGGGAGCCTTTA
GCTCTTGAAGGTGCTGATGAGGAAGGGGAGAGGGGAGGAGAAGGAATTTGTTTGTGAGATGGTCAGTGGG
CTGAATAGTGGTATGACCAAAAAGTGTTACTATAAATACACATAATCTGGAAAACAAAAATACTGTCATC
TCCTCCCTGCAAGGCGCTGTGATTAGGCAGGATGGAGCTTATTGCTGCAGTGTTAGAAAATGCATCCTTG
TAGTCCCAAAAAAGCCTGTTCCATCCTGCCCATCTCTTGTTCTCAATACTTCTTACTTCACGGTCACTCA
TTTTCTTCCTGTCCTTGGGTTGAGGTCTCAACTTCTTGTAATAGAATTTTTTCAGTTATAAGCGACAGAA
ATCCAACTCACACTATCTTAAGCAAAAAGGGGATTCACTGATACGTGTGTTAGGAAGGATATATGAAAGC
TCAAAGGTCAAGTGAAAAAAATGTAAGAACGAAGACCTTGGTGGGGTGTGGTGGCTCACGCCTATCATCC
CAGCATTTTGGGAGGCCGAGGCAGGTGGGTCACAAGGTCAGGAGTTCAAGACCAGCCTGCCCAAGATGGC
GAAACCCCATCTCTACTAAAAACACAAAAATTAGCCGGGTGTGGTGGCAGGCTCGTGTATTCCCAGCTAC
TTGGGAGGCTGAGGCAGAGAACTGTTTAAACCTGGGAGGCAGAGGTTGCAGTGAGTTGAGATGTGCCACT
GCACTCCAGCCTGGGCGGCAGAGTGAGACTCTGTCTCAAAAAAAAAACAAAAAAAAAAAACTAAGACCTT
GTGACTACTACCTACTACCTGGATCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCACCCCCCCACA
CTATCACCTCTCCTTGTTGTCAGTAGTTTCCTTTCTGCAGACAGGAGTTCCATGTGCTGGGAAGAGGGCC
ATTCAGAGCCTCGTATTCTCATCCTCTCAGTTTAGCAATGCGAGAAGAAAAAACTTTTGTCTCACAACCT
CATATACAATCTCAGAAATAGGCTCTTATTTTCTGGCTTGAGGCTGTCCAGAGGCACCAGGCACTGTGAT
GGTCTCACTTTCTGTCCTGGATCTATCTGTGGGGCCCAGACAGCAGGATCTATTTCAGAAAATAGGCGAG
AGAGGAAAAACTTATGTGGCCGTAAAAAACAGCGGTTTTCAAGTGGCCTATCCCCATCCACATCATAAAC
TTTTCTGCTGAGGCTTAAAAGTGCTTAGACTTCAAACTTGATCTAAAACAGAAATCCTACCTGGAAAAAT
CACCTTCCAGTCACTTAGCCAATCGCTCATCACTCTCTGTCTCTGAATCTCACCATGAGTTTCACACGTC
TCCCGAGAGAGCGTCTCCTTTATCATTACCACATGTGGAGTCAGCAGATTGGGTTTCATCTAAGCTCTGC
CTACCTACTATCCGAGTTCCCTAGCAGGTTAGTGACTTTCTCTGCCTTTTTGTTTCTTGATGTGAAAAGG
AACAACAGTGGCTGCTCACAGGGTTGTCAGTTACATGGTCAATTACATTACATGGACAATTCATGATGGT
GTCAGACCTGTCTGAGAAAAGGTGGCCCATGTTACCATGACAGGCCCCAAGGCTAACAGCCCCTTTCTGG
GTCATGGCTCATACAAAGGAGCCCTCCTTGGTTTGCTGGTGCTCTGAGACTTGCAAATGCATTAGGAATT
TTACACTGTAACCCGGTTTTAAATGGGTCCAGAGCATCCCCATTGCTAGACTACTGTGCTGAGGAAGGGC
ACTGGCTCATTGTTACATCCCATGAACACTCTGGGTCTCCTAGACCTCATCCTCTTTGAGCTTCTCTCTC
TCACTCTCTCTCTGCGCATTCAGGAGTGTACACATTTCTGTCCAGCACCCTGAAGTCTCTGGAAGAGAAG
GACCATATCCACCGAGTCCTGGACAAGATCACAGACACTTTGATCCACCTGATGGCCAAGGCAGGCCTGA
CCCTGCAGCAGCAGCACCAGCGGCTGGCCCAGCTCCTCCTCATCCTCTCCCACATCAGGCACATGAGGTG
AGGCATCTGTGGGCTTCCTACAGGAGAGACATAAAGAAAACATGCCCCCAAACCTATGTGACAGCTGGCC
GGGAAGGACTGGTGCCTGCATATGGAGAGTGCACTTGTGACAGTTCCTGGCATAGAATAAGCATAAATGC
TATAGGAGGACAGAAGAGAGAGGTTTAAATCTGCGAGGGTCACAGGGCAAGTGTCAGAGAAGGCATAGA
GGAAGCGATACTTACGCTTGGTTTAAAGCATGTGCTTTGGGGCAGTGGTTTAGAGATTGGGTGCAGTGTG
CAAATAGGAGGAGGGGGCCAATCAAGAGAAGTCAGTGAATGTACACATCCCCTGAAGACACTGGGTACAT
CTGTTATGGTCCCTGTGTACACTCGGATATTCTAAATGAGAGACCCTGGGGCCAGATGCCTCACGGAGAG
TCAATGTTGACTCCTTCATACCTGTTGAACCCCTTCTTGTCACCCCCATTGCCATTACCCTAGTCTAAGC
CACCATCATTTTCTGTTGGACTTCTGTGCCAGTCACTGGATGTGTATCCCTGCCTGTAATCTAGATCCTT
TCTAGATCATTCTCCATGATGTGTCCAGAGTGATCATTCTAGAACCAAATCTGATGTCATCCTCCTGCTT
AAAACCCTTAAGTTCTCATTGCTTTAGATAAAATATAAACCCTTTCACTTTGTTTTTATTACTCCTTAT
GATTCAGCCCTTACTTAGCTTACAAGGACTTCCTCATGTCTGAGCTCTAGCCATAATAGCTGACTGTTGG
ATGAGTCATCGGGGGGAGGTTCTTCTTCAGGCTGCAGATTGGCGGTCAGCCCTCCTGACCTCAGCTGGGC
TCACTCACACATCTGGGAGGCAGCTGCCTGAGGCCAGGGTGACTCTGCTCTATGCCTCATGTCTCCTATC
CTCCTTGTACCCACATGTTAGCTGGGACATGTTCTCATCGCAATGGCAGAGGCATGAGAAAGTGATCCTG
TTTGGGCAAGTGCATTTTACTCTTTTCTTTCACTCATGTCCACTGACATTTCATTGGCCAAGCAAGCATG
TGGGGTGTCCAGAGTCAAAGAGCGACATGTTGCCGGGGTCATGACTATTTCTGAGCAATAATCTAACCTA
TCATAGCTCAGATCTCACTCCTTGCAGGAAGCATCTCCTAATCCTTAAGACCTAGTTGGAACTTACACTC
TGTTCTTCCCTATGGTTACTGCCCATTTTACTATTTTTCTGCCCATTTAGACTGACAACTCTGTGAGCCA
TCATTGCAATATGGCTTGCTTACCCAATATCACCTAGCATGATGTAGAGCACATAGTAAATACTCAACAA
ATGTTTTCTGTAAGAGCTAAGGAAGGACATCAGCAGACAAAATAGAGTCTTTCTATGCCAAAAGGTGAAA
GTGGTCTCATTTCCATTCCATTGTCCTGTAATTTGGCTAGCCAAAAGCTTAGTGGATACCATTCCCATAA
GTAGACCTCATCTGCAGGGAAGAGATGGGGAGACTGCTGGGTTATTTATTGCAGACTCCAGCAGGACCAC
AACAATGATTCAAAGTGATGACACTAGAAGGACAGGTGCCAATGGGTGATGAAGCCACAATGACGATGTC
AAGTGGTATCACTAAAAGGACAGGTACTCATGGGTGATGAAGCCTACATGACCTTGGGCTTACACCAGGA
CCCTAGGAATGAAAGAGATTCCTTCTCTTAGTGGCTATGAGGGAAGGCCTATGATGTCTTAAGGAGGTTG
GATTCGATCATTTTTAAGGGACCTTCAAATCCTTAGACCGTGATTCAAATGGTAAGAAGTTTGCTCCATT
AAACTCCCAGGCACCACCCTTTCCGGAGACAACCTTTAAAAATTATTAGCTCCTGGGAAAATAGATGTAT
CTCATTTCTTTGTATCCCTCACAGTGCCATATGTGAAGACTTACATATGGTATATGCCCCCAACATTAC

FIGURE 1, page 91 of 93

TACTGAGTGAGTGAACAAAGAAATGAGGGAATGAATGGATGAACAAATGGCTCATGGCAGGCTTTTCCCT
GCCCTGTGAATTCGGCTTCTACTTGGTAAGAAGGTGATTGCAATCTCTGTTCTCAGGGTTCCCCAAGGAT
TCCTGTGTAACAGATGAAGGAATCACGTCTGTCAGGTAGAGTAGGTGACTGCATTCAGAGTATACATTTC
CAGTCTCCCCTGTCTTTTTCTTTTGATGAGTATTATAGAGAGGGAAGCCATGAGTGGATTAGATGCCAAA
ATCCCTGGCTGAGAGAATAACCTTACCCTGGAGGAAAACATATTAGCTTTGACTCTGAGCTGGGAATTTC
GGTGATGTTGTAGATTCAATGCATTGCAGTTGGGTGTTTTTATTTGTTGAAAGGAATTGCTGAATTTTCA
AATCCATTAACTGCTTGTCAGCATTAGCAAGCCTAATTAGTTAATACTAAGTAAATTTGCACTAAATATA
CAACCCTGGCTGATTTTACTGGCCACGTCTGGCAGAGGGCAGCAGCAGGGAGAAAGCTCTGTAGAGTTTC
TGTTGGAATCGTGTGAAAAGCTGGAGAGGTTGCTTCTCTTTCTCTCTCTCTCTCTTTCTCTCTCTCTCTC
TGACACACACACACACATACACACACACACAATTGTAATAATAATAATATTTTGGTTCCTCACTAAGCCA
ATCTAAATCGCAGAAGTCTATTTTGTTAAGTAAGCTTGGCCCCAGCCATATGTTGCTACTCAGAGAATTT
AATATCAGATTTCATCTGACTGTAAACGTGAATCATCAGGTTGCACAAGGAACACAGTGGCAGATCCAGG
GGGCATTTAACTTTTATAGCATTTTAAATGAAAAAAAAAAAAAAGTAACACTTAAACAAGTAATTTAGATC
ATGCTGTAGGCCCTGAATAGCTTTGATGTTGTGTTTTCATGGCAAGTCTCCAACTTGAGCTGAATTTTCC
CCTACTAAAAATGCAAATTTTTCTAAGACCTTCTCTTGGTCCTGCTACTCATGATACATATTTCTTTTAA
AAGAAATTTCAAACTAGATAATAGTTGTTCTCCTCCCCACCCCCGCCACCAGTAGTGTGGTGGGGCAGCA
GAGTTGTGGCTAGTGGAGGAGAGCAGAGGAGGAGAGTAGGGAAAGGAGAATGCCATTTGCCTACATTTCC
CTCTGCCCATTTCCCCCTGCCCATTTCCCCCCTTGTTTTCCTGAACGTGAACTGAGCTCTGGGCACTGTT
TTAGGCCTAGCAGGGGACAGGATAAAGCCTGCTTCTCTAGGAATTCGCACTGAGGGTGTGAGTGTGTGCA
CGTGTGTGTTTGGAGGCGGGAGAATAAACACAAATAAATAAAAAGGAGAATTTCAGGCAGTGATAAGAGT
GCTGAGAAAAACAGAACGGTGTGAAAGAGGAAGGCTGAGCCTGCAGAGGCTTGAGGCTGCTGCCACTGGG
TAGCGGTAGGCCTTTCCGAGGAGGCGGCATTTGAAGACCGGAGGAAGGTTCATGCCAGCAAGTAGGAACA
GCAAGTGTAGGTCCCCTAAGTCTTGGGGGAGCTTAGTTCCTTTAAGGGCAGCACAAAAATCAGTGTGGCT
CCGGAGAGCACATTAGGGGAGAGAGGCAGGAAGAGCTTGGAGACATGGATGGAAGCTGGACCAGTTGGGC
CTTGTTGAACATGGAAAGGCATTTAGATCGTATTCTGAGTTAAATGGGAAGTGACGTGAGAGATTTAACA
ATGGAGCGTCTTGAACTGCTTTACTCATTTAAAATACCCACTCCTGCTTGGCTGAATATCTCATGTTGTC
TTTTTAGAAGCTTTGGCGATCCTATTTGAATGCATTTAGGTCCTATTGGAGGGGAATAGGATCTCATTTG
AGGCCACGGAGGTCCATGGAAGTCACCTGCATAGCAAATACCCTGAAAGTGGCTGCAGGGAGAGTGTGAG
GGTGGGACCGCCCTGGTAGGAGGTGGAAAATGAAAAACACACGGCCATGAGTTCCAGATTAGGGCTTCTG
AAAGCCCTCAGCTTTCCCAGCTCCCATCCTAAAGTGGGTCTTTAAACAGGAAGAAAGAAAGATTGCTAAG
TGTCTTTGGAGTTCCTCTTCCTTCCCCTTCTAGGGATTTCAGCACTCCTGGGGCTCGGGTTGGCTCTAAA
GTAGTCCTTTCTGTGTCTTCCCACCTACAGTAACAAAGGCATGGAGCATCTGTACAGCATGAAGTGCAAG
AACGTGGTGCCCCTCTATGACCTGCTGCTGGAGATGCTGGACGCCCACCGCCTACATGCGCCCACTAGCC
GTGGAGGGGCATCCGTGGAGGAGACGGACCAAAGCCACTTGGCCACTGCGGGCTCTACTTCATCGCATTC
CTTGCAAAAGTATTACATCACGGGGGAGGCAGAGGGTTTCCCTGCCACGGTCTGAGAGCTCCCTGGCTCC
CACACGGTTCAGATAATCCCTGCTGCATTTTACCCTCATCATGCACCACTTTAGCCAAATTCTGTCTCCT
GCATACACTCCGGCATGCATCCAACACCAATGGCTTTCTAGATGAGTGGCCATTCATTTGCTTGCTCAGT
TCTTAGTGGCACATCTTCTGTCTTCTGTTGGGAACAGCCAAAGGGATTCCAAGGCTAAATCTTTGTAACA
GCTCTCTTTCCCCCTTGCTATGTTACTAAGCGTGAGGATTCCCGTAGCTCTTCACAGCTGAACTCAGTCT
ATGGGTTGGGGCTCAGATAACTCTGTGCATTTAAGCTACTTGTAGAGACCCAGGCCTGGAGAGTAGACAT
TTTGCCTCTGATAAGCACTTTTTAAATGGCTCTAAGAATAAGCCACAGCAAAGAATTTAAAGTGGCTCCT
TTAATTGGTGACTTGGAGAAAGCTAGGTCAAGGGTTTATTATAGCACCCTCTTGTATTCCTATGGCAATG
CATCCTTTTATGAAAGTGGTACACCTTAAAGCTTTTATATGACTGTAGCAGAGTATCTGGTGATTGTCAA
TTCACTTCCCCCTATAGGAATACAAGGGGCCACACAGGGAAGGCAGATCCCCTAGTTGGCCAAGACTTAT
TTTAACTTGATACACTGCAGATTCAGAGTGTCCTGAAGCTCTGCCTCTGGCTTTCCGGTCATGGGTTCCA
GTTAATTCATGCCTCCCATGGACCTATGGAGAGCAACAAGTTGATCTTAGTTAAGTCTCCCTATATGAGG
GATAAGTTCCTGATTTTTGTTTTTATTTTTGTGTTACAAAAGAAAGCCCTCCCTCCCTGAACTTGCAGTA
AGGTCAGCTTCAGGACCTGTTCCAGTGGGCACTGTACTTGGATCTTCCCGGCGTGTGTGTGCCTTACACA
GGGGTGAACTGTTCACTGTGGTGATGCATGATGAGGGTAAATGGTAGTTGAAAGGAGCAGGGGCCCTGGT
GTTGCATTTAGCCCTGGGGCATGGAGCTGAACAGTACTTGTGCAGGATTGTTGTGGCTACTAGAGAACAA
GAGGGAAAGTAGGGCAGAAACTGGATACAGTTCTGAGCACAGCCAGACTTGCTCAGGTGGCCCTGCACAG
GCTGCAGCTACCTAGGAACATTCCTTGCAGACCCCGCATTGCCTTTGGGGGTGCCCTGGGATCCCTGGGG
TAGTCCAGCTCTTATTCATTTCCCAGCGTGGCCCTGGTTGGAAGAAGCAGCTGTCAAGTTGTAGACAGCT
GTGTTCCTACAATTGGCCCAGCACCCTGGGGCACGGGAGAAGGGTGGGGACCGTTGCTGTCACTACTCAG
GCTGACTGGGGCCTGGTCAGATTACGTATGCCCTTGGTGGTTTAGAGATAATCCAAAATCAGGGTTTGGT
TTGGGGAAGAAAATCCTCCCCCTTCCTCCCCCGCCCCGTTCCCTACCGCCTCCACTCCTGCCAGCTCATT
TCCTTCAATTTCCTTTGACCTATAGGCTAAAAAAGAAAGGCTCATTCCAGCCACAGGGCAGCCTTCCCTG
GGCCTTTGCTTCTCTAGCACAATTATGGGTTACTTCCTTTTTCTTAACAAAAAAGAATGTTTGATTTCCT
CTGGGTGACCTTATTGTCTGTAATTGAAACCCTATTGAGAGGTGATGTCTGTGTTAGCCAATGACCCAGG
TAGCTGCTCGGGCTTCTCTTGGTATGTCTTGTTTGGAAAAGTGGATTTCATTCATTTCTGATTGTCCAGT
TAAGTGATCACCAAAGGACTGAGAATCTGGGAGGGCAAAAAAAAAAAAAAAAGTTTTTATGTGCACTTAA
ATTTGGGGACAATTTTATGTATCTGTGTTAAGGATATGCTTAAGAACATAATTCTTTTGTTGCTGTTTGT
TTAAGAAGCACCTTAGTTTGTTTAAGAAGCACCTTATATAGTATAATATATATATTTTTTTGAAATTACATT
GCTTGTTTATCAGACAATTGAATGTAGTAATTCTGTTCTGGATTTAATTGACTGGGTTAACATGCAAAA
ACCAAGGAAAAAATATTTAGTTTTTTTTTTTTTTTGTATACTTTTCAAGCTACCTTGTCATGTATACAG
TCATTTATGCCTAAAGCCTGGTGATTATTCATTTAAATGAAGATCACATTTCATATCAACTTTTGTATCC
ACAGTAGACAAAATAGCACTAATCCAGATGCCTATTGTTGGATATTGAATGACAGACAATCTTATGTAGC
AAAGATTATGCCTGAAAAGGAAAATTATTCAGGGCAGCTAATTTTGCTTTTACCAAAATATCAGTAGTAA
TATTTTTGGACAGTAGCTAATGGGTCAGTGGGTTCTTTTTAATGTTTATACTTAGATTTTCTTTTAAAAA
AATTAAAATAAAACAAAAAAAATTTCTAGGACTAGACGATGTAATACCAGCTAAAGCCAAACAATTATAC
AGTGGAAGGTTTTACATTATTCATCCAATGTGTTTCTATTCATGTTAAGATACTACTACATTTGAAGTGG
GCAGAGAACATCAGATGATTGAAATGTTCGCCCAGGGGTCTCCAGCAACTTTGGAAATCTCTTTGTATTT

FIGURE 1, page 92 of 93

TTACTTGAAGTGCCACTAATGGACAGCAGATATTTTCTGGCTGATGTTGGTATTGGGTGTAGGAACATGA
TTTAAAAAAAAAACTCTTGCCTCTGCTTTCCCCCACTCTGAGGCAAGTTAAAATGTAAAAGATGTGATTT
ATCTGGGGGGCTCAGGTATGGTGGGGAAGTGGATTCAGGAATCTGGGGAATGGCAAATATATTAAGAAGA
GTATTGAAAGTATTTGGAGGAAAATGGTTAATTCTGGGTGTGCACCAAGGTTCAGTAGAGTCCACTTCTG
CCCTGGAGACCACAAATCAACTAGCTCCATTTACAGCCATTTCTAAAATGGCAGCTTCAGTTCTAGAGAA
GAAAGAACAACATCAGCAGTAAAGTCCATGGAATAGCTAGTGGTCTGTGTTTCTTTTCGCCATTGCCTAG
CTTGCCGTAATGATTCTATAATGCCATCATGCAGCAATTATGAGAGGCTAGGTCATCCAAAGAGAAGACC
CTATCAATGTAGGTTGCAAAATCTAACCCCTAAGGAAGTGCAGTCTTTGATTTGATTTCCCTAGTAACCT
TGCAGATATGTTTAACCAAGCCATAGCCCATGCCTTTTGAGGGCTGAACAAATAAGGGACTTACTGATAA
TTTACTTTTGATCACATTAAGGTGTTCTCACCTTGAAATCTTATACACTGAAATGGCCATTGATTTAGGC
CACTGGCTTAGAGTACTCCTTCCCCTGCATGACACTGATTACAAATACTTTCCTATTCATACTTTCCAAT
TATGAGATGGACTGTGGGTACTGGGAGTGATCACTAACACCATAGTAATGTCTAATATTCACAGGCAGAT
CTGCTTGGGGAAGCTAGTTATGTGAAAGGCAAATAAAGTCATACAGTAGCTCAAAAGGCAACCATAATTC
TCTTTGGTGCAAGTCTTGGGAGCGTGATCTAGATTACACTGCACCATTCCCAAGTTAATCCCCTGAAAAC
TTACTCTCAACTGGAGCAAATGAACTTTGGTCCCAAATATCCATCTTTTCAGTAGCGTTAATTATGCTCT
GTTTCCAACTGCATTTCCTTTCCAATTGAATTAAAGTGTGGCCTCGTTTTTAGTCATTTAAAATTGTTTT
CTAAGTAATTGCTGCCTCTATTATGGCACTTCAATTTTGCACTGTCTTTTGAGATTCAAGAAAAATTTCT
ATTCATTTTTTTGCATCCAATTGTGCCTGAACTTTTAAAATATGTAAATGCTGCCATGTTCCAAACCCAT
CGTCAGTGTGTGTGTTTAGAGCTGTGCACCCTAGAAACAACATACTTGTCCCATGAGCAGGTGCCTGAGA
CACAGACCCCTTTGCATTCACAGAGAGGTCATTGGTTATAGAGACTTGAATTAATAAGTGACATTATGCC
AGTTTCTGTTCTCTCACAGGTGATAAACAATGCTTTTTGTGCACTACATACTCTTCAGTGTAGAGCTCTT
GTTTTATGGGAAAAGGCTCAAATGCCAAATTGTGTTTGATGGATTAATATGCCCTTTTGCCGATGCATAC
TATTACTGATGTGACTCGGTTTTGTCGCAGCTTTGCTTTGTTTAATGAAACACACTTGTAAACCTCTTTT
GCACTTTGAAAAAGAATCCAGCGGGATGCTCGAGCACCTGTAAACAATTTTCTCAACCTATTTGATGTTC
AAATAAAGAATTAAACT

FIGURE 1, page 93 of 93

SNP Position	Reference Sequence & SNP Position Number[1]	Nucleotide Change	AA Change	Frequency in Liverpool		Number of individuals with a change in heterozygosity[2]	Number of individuals with a loss in heterozygosity[3]	In which Populations observed[4]
				Blood.	Tumor			
Exon 1A *	170035	C to A (ACTTGCTCCCG)	None (5'UTR)	0/84 0%	0/92 0%	0	0	3(C)
Exon 1A	170068	G to T (CGCAGGCTCCC)	None (5'UTR)	1/88 1%	1/94) 1%	0	0	2
Exon 1A	170256	T to C (GCATCTGGGAT)	Silent (Ser-Ser)	45/90 50%	52/94 55%	6	0	2, 3(all), 6
Exon 1A	170368	A to G (GCAGCAAGCCC)	Lys-Glu	1/92 1%	1/96 1%	0	0	2, 3(A)
Exon 1A	170487	G to C (GCTGCGGCGTT)	Silent (Ala-Ala)	7/90 8%	12/94 13%	4	0	2, 3(N,C,A), 6
Exon 1B	169812	C to G (AGCAGCGACGA)	None (5'-UTR)	1/96 1%	1/96 1%	0	0	2, 3(A,S)
Exon 1B	169823	A to G (CAAGTAAAGTA)	None (5'-UTR)	1/96 1%	1/96 1%	0	0	2
Intron 1D	167950	C to G (CTTCCCGAATC)	None (-59 promoter)	2/96 2%	2/96 2%	0	0	2
Intron 1D	167989	T to G (CACACTCTCTC)	None (-20 promoter)	15/96 17%	16/96 17%	3	0	2, 3(all)
Exon 1C	168054	C to G (TCTCACTCTCT)	None (5'-UTR)	1/96 1%	1/96 1%	0	0	2
Intron 1E	64331	A to G (TCCGTAAATTG)	None (+ 42 intron)	35/96 36%	36/96 38%	4	0	2, 3(N,I,A,S)
Exon 1F	52901	G to A (CTATAGCATAA)	None (5'-UTR)	0/74 0%	0/78 0%	0	0	3(A)
Exon 1F	52877	C to A (CCATGCTCCTT)	None (5'-UTR)	2/72 3%	0/78 0%	0	0	2, 3(N)
Exon 1G 5' genomic *	18783	C to T (TGAGACGATTG)	None (-42 inton)	0/96 0%	0/96 0%	0	0	3 (A)
Exon 1G 5' genomic *	18937	A to C (GTTCCAAGCAG)	None (-4 intron)	0/96 0%	0/96 0%	0	0	3 (C)
Intron 1G *	19034	T to C (GAAGGTAAGTT)	None (+2 intron)	1/96 1%	0/96 0%	1	0	2
Intron 3	243187	T to C TTTTTTCTTTT	None (+101 intron)	39/96 41%	36/96 38%	3	0	2, 3(all)

FIGURE 2a, sheet 1 of 4

SNP Position	Reference Sequence & SNP Position Number[1]	Nucleotide Change	AA Change	Frequency in Liverpool		Number of individuals with a change in heterozygosity[2]	Number of individuals with a loss in heterozygosity[3]	In which Populations observed[4]
				Blood.	Tumor			
Exon 3	243055	C to T CTCCGCAAATG	Silent (Arg-Arg)	2/96 2%	3/96 3%	1	0	2, 6
Exon 4	306292	G to A (AGCCCGCTCAT)	Silent (Pro-Pro)	1/96 1%	1/94 1%	0	0	2
Exon 4	306382	C to G (CCCCCCATACT)	Silent (Pro-Pro)	17/96 18%	16/94 17%	4	0	2, 3(C,I,S),6
Exon 6 *	423067	T to C (TTGTGTGCCTC)	Cys-Arg	0/96 0%	0/96 0%	0	0	3(N)
Intron 6	423149	T to G (TTGTATTTTTC)	None (+52 intron)	11/96 11%	12/96 13%	0	0	2, 3(N,C,I,A)
Intron 6	423163	A to G (CAGATACGATC)	None (+66 intron)	10/96 10%	10/96 10%	1	0	2, 3(N,C,I,A)
Intron 6	423220	G to A (CACACGTTTTA)	None (+123 intron)	29/96 30%	29/96 30%	3	1	2, 3(N,C,I,A)
Intron 6	423232	C to G (AATAACCTACC)	None (+135 intron)	2/96 2%	2/96 2%	0	0	2
Intron 6	423258	A to G (TTATAAAGGTA)	None (+161 intron)	12/84 13%	11/96 12%	0	0	2, 3(N,C,I,A)
Intron 8	459706	G to C (TTCCCGCTGCC)	None (-994 intron)	seq in	Coriell only	n/a	n/a	3(I)
Intron 8	459832	G to A (TGCACGTGTGT)	None (-868 intron)	seq in	Coriell only	n/a	n/a	3(S)
Intron 8	459913	A to G (AAAACAGAACG)	None (-787 intron)	seq in	Coriell only	n/a	n/a	3(N,I)
Intron 8	460024	C to G (TTCATCCCAGC)	None (-676 intron)	seq in	Coriell only	n/a	n/a	3(all)
Intron 8	460056	C to T (GTCCCCTAAGT)	None (-644 intron)	seq in	Coriell only	n/a	n/a	3(I)
Intron 8 *	460159	A to G (CATGGATGGAA)	None (-541 intron)	seq in	Coriell only	n/a	n/a	3(S)
Intron 8	460553	T to C (CAGCTTCCATC)	None (-147 intron)	2/82 2%	4/92 4%	0	0	2, 3(I)
Intron 8	460564	G to A (CTAAAGTGGGT	None (-136 intron)	82/82 0%	91/92 1%	1	0	2

FIGURE 2a, sheet 2 of 4

SNP Position	Reference Sequence & SNP Position Number[1]	Nucleotide Change	AA Change	Frequency in Liverpool Blood.	Frequency in Liverpool Tumor	Number of individuals with a change in heterozygosity[2]	Number of individuals with a loss in heterozygosity[3]	In which Populations observed[4]
Exon 8	460929	A to G (GCCACAGTCTG	Silent (Thr-Thr)	76/96 80%	83/96 86%	3	0	1, 2, 3(all), 5, 6
Exon 8	461199	T to C (GAGGATTCCCG)	None (3'UTR)	1/88 1%	1/94 1%	0	0	2
Exon 8	461231	A to G (AGTCTATGGGT)	None (3'UTR)	1/90 1%	1/94 1%	0	0	2
Exon 8	461337	A to C (CTAAGAATAAG)	None (3'-UTR)	0/90 0%	0/94 0%	0	0	3(A)
Exon 8	461520	G to C (ATTCCGCCTAT)	None (3'-UTR)	3/92 3%	3/96 3%	0	0	2
Exon 8	461843	G to A CCGGCGTGTGT	None (3'-UTR)	1/90 1%	1/96 1%	0	0	2
Exon 8	461968	T to C (AGTACTTGTGC)	None (3'-UTR)	43/89 48%	46/94 49%	3	2	2, 3(all)
Exon 8	462125	C to T (GGTGCCCTGGG)	None (3'-UTR)	0/92 0%	0/94 0%	0	0	3(A)
Exon 8 *	462398	G to A (CTACCGCCTCC)	None (3'-UTR)	0/84 0%	0/94 0%	0	0	3(A)
Exon 8	462683	C to A (TCATTCATTTC)	None (3'-UTR)	3/92 3%	5/96 5%	2	1	2, 3(I,A,S)
Exon 8	462949	T to G (TGTTCTGGATT)	None (3'UTR)	0/82 0%	0/96 0%	0	0	3(A,S)
Exon 8	463958	T to C (TTGCCTAGCTT)	None (3'-UTR)	5/80 6%	4/90 4%	1	0	2, 3(N)
Exon 8	463966	C to T (CTTGCCGTAAT)	None (3'-UTR)	1/82 1%	1/90 1%	0	0	2, 3(N)
Exon 8	464237	G to A (GCCTCGTTTTT)	None (3'-UTR)	2/90 2%	2/94 2%	0	0	2
Exon 8	464735	A to T (TATTCATTTTT)	None (3'-UTR)	9/90 10%	4/96 4%	1	0	2, 3(N,C,I,A)
Exon 8 *	465074	T to C GCCGATGCATA	None (3'-UTR)	0/84 0%	0/94 0%	0	0	3(N,C,I,A)
Exon 8	AL078582 (54404)	A to G (ATCAAAGTGGT)	None (3'-flanking)	20/78 26%	23/88 26%	5	2	2, 3(N,C,I,A)

FIGURE 2a, sheet 3 of 4

SNP Position	Reference Sequence & SNP Position Number[1]	Nucleotide Change	AA Change	Frequency in Liverpool		Number of individuals with a change in heterozygosity[2]	Number of individuals with a loss in heterozygosity[3]	In which Populations observed[4]
				Blood.	Tumor			
Exon 8	AL078582 (54460)	C to A CTCACCTCACT	None(3'-flanking)	3/76 4%	2/76 3%	0	0	2, 3(C,I,N)

* SNPs in Liverpool clinical tissue samples. Seen only one time and may represent sequencing artifacts. They are not included in the total counts of SNPs.

1. The SNP position number in the parenthesis is based on the beginning of each exon as 1. For SNPs within the introns, - sign was used for the ones in upstream introns and + sign for downstream introns referring the first base of the intron adjacent to the exon as 1.

2. For some heterozygosity calculations, individuals 47 and 48 were excluded because it is believed that the blood or the tumor sample was switched. These excluded cases were t=when both individuals showed a change in heterozygosity.

3. Loss of heterozygosity calculation includes any case where a heterozygous blood genotype became a homozygous genotype of the minor allele in the same individual's tumor sample. A change from a homozygous genotype of the major allele in the blood sample into a homozygous genotype of the minor allele in the tumor sample would also be counted

4. Code is as follows
   1: SNP discovered in cDNA SNP project
   2: SNP discovered in Liverpool DNA
   3: SNP discovered in Coriell (N=Northern European, C=Chinese, I=Indo-Pakistani, A=African American, S=Southwestern Native American)
   4: SNP discovered in CEPH
   5: Roodi N., Bailey R., Kao W. Y., Verrier C., Yee C., Dupont W., and Parl F. F. J. Natl. Cancer Inst. 87 (1995) 446-451.
   6: Parl, Fritz, Estrogens, Estrogen Receptor and Breast Cancer, IOS Press: Amsterdam, 2000.
   Andersen TI et al. Human Mutation (1997) 9:531-536 : G to T at 838 of x03635

FIGURE 2a, sheet 4 of 4

SNP Position	Reference Sequence & SNP Position #	Nucleotide Change	AA Change	Coriell Frequencies					Liverpool Frequencies	
				N.Eur	Chi	In-Pk	Af/Am	SW-NA	Blood	Tumor
Exon 1A *	170035	C to A ACTTGCTCCGT	None (5'UTR)	0/20 0%	1/20 5%	0/20 0%	0/18 0%	0/20 0%	0/84 0%	0/92 0%
Exon 1A	170068	G to T CGCAGGCTCCC	None (5'UTR)	0/20 0%	0/20 0%	0/20 0%	0/18 0%	0/20 0%	1/88 1%	1/94 1%
Exon 1A	170256	T to C (GCATCTGGGAT)	Silent (Ser-Ser)	11/20 55%	10/20 50%	10/20 50%	9/18 50%	5/20 25%	45/90 50%	52/94 55%
Exon 1A	170368	A to G GCAGCAAGCCC	Lys-Glu	0/20 0%	0/20 0%	0/20 0%	0/18 0%	0/20 0%	1/92 1%	1/96 1%
Exon 1A	170487	G to C (GCTGCGGCGTT)	Silent (Ala-Ala)	2/20 10%	1/20 5%	0/20 0%	1/18 6%	0/20 0%	7/90 8%	12/94 13%
Exon 1B	169812	C to G (AGCAGCGACGA)	None (5'-UTR)	0/20 0%	0/20 0%	0/20 0%	2/20 10%	4/20 20%	1/96 1%	1/96 1%
Exon 1B	169823	A to G (CAAGTCAGTG)	None (5'-UTR)	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0/20 0%	1/96 1%	1/96 1%
Intron 1D	167950	C to G (CTTCCCGAATC)	None (-59 promoter)	0/16 0%	0/20 0%	0/20 0%	0/18 0%	0/18 0%	2/96 2%	2/96 2%
Intron 1D	167989	T to G (CACACTCTCTC)	None (-20 promoter)	1/18 5%	5/20 25%	5/20 25%	7/18 39%	5/18 28%	15/96 17%	16/96 17%
Exon 1C	168054	C to G (TCTCACTCTCT)	None (-6 promoter)	0/18 0%	0/20 0%	0/20 0%	0/18 0%	0/18 0%	1/96 1%	1/96 1%
Intron 1E	64331	C to T (CAATTCACGGA)	None (+ 42 intron)	5/11 45%	0/16 0%	5/18 28%	4/18 22%	2/16 13%	35/96 36%	36/96 38%
Exon 1F *	52901	C to T (TTATGCTATAG)	None (-44 promoter)	0/20 0%	0/20 0%	0/20 0%	1/18 6%	0/16 0%	0/74 0%	0/78 0%
Exon 1F	52877	G to T (AAGGAGCATGG)	None (-68 promoter)	1/20 5%	0/20 0%	0/20 0%	0/18 0%	0/16 0%	2/72 3%	0/78 0%
Exon 1G Promoter Region *	18783	C to T (TGAGACGATTG)	None (-42 inton)	0/20 0%	0/20 0%	0/20 0%	1/20 5%	0/20 0%	0/96 0%	0/96 0%
Exon 1G Promoter Region *	18937	A to C (GTTCCAAGCAG)	None (-4 intron)	0/20 0%	1/20 5%	0/20 0%	0/20 0%	0/20 0%	0/96 0%	0/96 0%
Intron 1G *	19034	T to C (GAAGGTAAGTT)	None (+2 intron)	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0/20 0%	1/96 1%	0/96 0%
Intron 3	243187	T to C TTTTTTCTTTT	None (+101 intron)	12/18 67%	6/20 30%	5/20 25%	5/18 28%	2/16 13%	39/96 41%	36/96 38%

FIGURE 2b, sheet 1 of 3

SNP Position	Reference Sequence & SNP Position #	Nucleotide Change	AA Change	Coriell Frequencies					Liverpool Frequencies	
				N.Eur	Chi	In-Pk	Af/Am	SW-NA	Blood	Tumor
Exon 3	243055	C to T CTCCGCAAATG	Silent (Arg-Arg)	0/18 0%	0/20 0%	2/20 10%	0/20 0%	0/18 0%	2/96 2%	3/96 3%
Exon 4	306292	G to A (AGCCCGCTCAT)	Silent (Pro-Pro)	0/8 0%	0/14 0%	0/14 0%	0/2 0%	0/12 0%	1/96 1%	1/94 1%
Exon 4	306382	C to G CCCCCCATACT	Silent (Pro-Pro)	0/8 0%	14/16 25%	14/16 25%	0/6 0%	2/13 15%	17/96 18%	16/94 17%
Exon 6 *	423067	T to C (TTGTGTGCCTC)	Cys-Arg	1/20 5%	0/20 0%	0/20 0%	0/20 0%	0/16 0%	0/96 0%	0/96 0%
Intron 6	423149	T to G (TTGTATTTTTC)	None (+52 intron)	3/20 15%	7/20 35%	2/18 11%	6/20 30%	0/16 0%	11/96 11%	12/96 13%
Intron 6	423163	A to G (CAGATACGATC)	None (+66 intron)	1/20 5%	6/20 30%	2/20 10%	3/20 15%	0/16 0%	10/96 10%	10/96 10%
Intron 6	423220	G to A (CACACGTTTTA)	None (+123 intron)	4/20 20%	5/20 25%	8/20 40%	7/20 35%	0/16 0%	29/96 30%	29/96 30%
Intron 6	423232	C to G (AATAACCTACC)	None (+135 intron)	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0/16 0%	2/96 2%	2/96 2%
Intron 6	423258	A to G (TTATAAAGGTA)	None (+161 intron)	3/20 15%	7/20 35%	3/20 15%	6/20 30%	0/16 0%	12/84 13%	11/96 12%
Intron 8	459706	G to C (TTCCCGCTGCC)	None (-994 intron)	16/16 100%	14/14 100%	20/20 100%	15/16 94%	5/5 100%	seq only	in Coriell
Intron 8	459832	G to A (TGCACGTGTGT)	None (-868 intron)	0/20 0%	0/18 0%	0/20 0%	0/16 0%	1/16 6%	seq only	in Coriell
Intron 8	459913	A to G (AAAACAGAACG	None (-787 intron)	1/20 5%	0/18 0%	0/20 0%	1/16 6%	0/16 0%	seq only	in Coriell
Intron 8	460024	C to G (TTCATCCCAGC)	None (-676 intron)	6/20 30%	4/18 22%	5/18 28%	11/16 69%	4/12 33%	seq only	in Coriell
Intron 8 *	460056	C to T (CTAAGAATAAG)	None (-644 intron)	0/20 0%	0/18 0%	0/20 0%	1/16 6%	0/12 0%	seq only	in Coriell
Intron 8 *	460159	A to G (CATGGATGGAA)	None (-531 intron)	0/20 0%	0/18 0%	0/20 0%	0/14 0%	1/12 8%	seq only	in Coriell
Exon 8	460553	C to T (CAGCTCCCATC)	None (-147 intron)	0/16 0%	0/18 0%	1/20 5%	0/18 0%	0/20 0%	2/82 2%	4/92 4%
Exon 8	460564	G to A (CTAAAGTGGGT	None (-136 intron)	16/16 100%	18/18 100%	18/18 100%	18/18 100%	20/20 100%	82/82 100%	91/92 99%
Exon 8	460929	A to G (GCCACAGTCTG	Silent (Thr-Thr)	16/20 80%	17/20 15%	16/20 80%	16/20 80%	14/20 70%	76/96 80%	83/96 86%

FIGURE 2b, sheet 2 of 3

SNP Position	Reference Sequence & SNP Position #	Nucleotide Change	AA Change	Coriell Frequencies					Liverpool Frequencies	
				N.Eur	Chi	In-Pk	Af/Am	SW-NA	Blood	Tumor
Exon 8	461199	T to C (GAGGATTCCCG)	None (3' UTR)	0/18 0%	0/18 0%	0/20 0%	0/18 0%	0/20 0%	1/88 1%	1/94 1%
Exon 8	461231	A to G (AGTCTATGGGT)	None (3' UTR)	0/18 0%	0/18 0%	0/20 0%	0/18 0%	0/20 0%	1/90 1%	1/94 1%
Exon 8	461337	A to C (CTAAGAATAAG)	None (3'-UTR)	0/18 0%	0/18 0%	0/20 0%	3/18 17%	0/20 0%	0/90 0%	0/94 0%
Exon 8	461520	G to C (ATTCCGCCTAT)	None (3' UTR)	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0/20 0%	3/92 3%	3/96 3%
Exon 8	461843	G to A CCGGCGTGTGT	None (3' UTR)	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0/20 0%	1/90 1%	1/96 1%
Exon 8	461968	T to C (AGTACTTGTGC)	None (3'-UTR)	9/20 45%	8/20 40%	13/20 60%	11/20 55%	7/20 35%	43/89 48%	46/94 49%
Exon 8	462125	C to T (GGTGCCCTGGG)	None (3'-UTR)	0/20 0%	0/20 0%	0/20 0%	2/20 10%	0/20 0%	0/92 0%	0/94 0%
Exon 8 *	462398	G to A (CTACCGCCTCC)	None (3'-UTR)	0/20 0%	0/20 0%	0/20 0%	1/20 5%	0/20 0%	0/84 0%	0/94 0%
Exon 8	462683	C to A (TCATTCATTTC)	None (3'-UTR)	0/20 0%	2/20 10%	1/20 5%	1/20 5%	7/20 35%	3/92 3%	5/96 5%
Exon 8	462949	T to G (TGTTCTGGATT)	None (3'UTR)	0/20 0%	0/20 0%	0/20 0%	1/20 5%	1/20 5%	0/82 0%	0/96 0%
Exon 8	463958	T to C (TTGCCTAGCTT)	None (3'-UTR)	2/20 10%	0/20 0%	0/20 0%	0/20 0%	0/20 0%	5/80 6%	4/90 4%
Exon 8	463966	C to T (CTTGCCGTAAT)	None (3'-UTR)	0/20 0%	0/20 0%	0/18 0%	0/16 0%	0/20 0%	1/82 1%	1/90 1%
Exon 8	464237	G to A (GCCTCGTTTTT)	None (3'-UTR)	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0/20 0%	2/90 2%	2/94 2%
Exon 8	464735	A to T (TATTCATTTTT)	None (3'-UTR)	2/20 10%	2/20 10%	1/20 5%	0/20 0%	8/20 40%	9/90 10%	4/96 4%
Exon 8 *	465074	T to C GCCGATGCATA	None (3'-UTR)	0/20 0%	1/20 5%	0/20 0%	0/20 0%	0/20 0%	0/84 0%	0/94 0%
Exon 8	AL078582 (54404)	A to G (ATCAAAGTGGT)	None (3'-flanking)	3/20 15%	2/18 22%	3/20 15%	1/14 7%	0/20 0%	20/78 26%	23/88 26%
Exon 8	AL078582 (54460)	C to A CTCACCTCACT	None (3'-flanking)	0/18 0%	1/16 14%	1/18 6%	0/10 0%	7/20 35%	3/76 4%	2/76 3%

*. SNPs in Coriell Diversity panels. Seen only one time and may represent sequencing artifacts. They are not included in the total counts of SNPs.

FIGURE 2b, sheet 3 of 3

FIGURE 2c

PCR primers

Exon	Primer Position	PCR Product Length (bp)	Forward Primer	Reverse Primer
1A	ER1ixAF-1. ER1ixAR-1	930	M13f-GCTCGTTCTCCAGGTAGTAGGGCA	M13r-GGGGCACATAAGGCAGCACA
1B	-161/ exon1B /+154	472	TGCAACCGCACACCCCATTCTATCTG	GGGCCTCCAACTTTAAGTACTGGTCTCC
1C	-227/ exon1C /+107	445	GGTTTCTCCTCCCCAGTACAGCTTTC	AGAACAGCAATCCTCATCTCCCTGC
1D	-225/ exon1D /+123	444	TCTCAAAGGGAGTGGCCGAAATGC	TACTGTGCTACGCCGACTTTCCTC
1E	-187/ exon1E /+163	472	AGCCAAACATTGATTCTTCAGTGCC	AAGCAACGCATGTAGAGTGCCC
1F	-316/ exon 1F /+144	587	GCAAAATATCCTTGGAGCAGAAAGAC	TTTCCAACTCCACATGCCTGTC
1G	18711/ exon 1G / 19200	489	TTGGCCAACATTTTCCCTCA	TCCCACAGCCTTGTCTTGGT
2	-170/ exon2 /+240	600	ATAGGCAACACCTTTTGCTGCAACAG	ATTGAGTCTTGCCAAAGGAAGGAAGC
3	exon 3	483	CACTTCAAGAAGGACAGAAAAAGGCA	TTAGAATTTCCAGTTCCAGACACTTCCA
4	-156/ exon4 /+103	602	GCCACTTGTGTGAACACCTTACCG	CATGTGTATTGCGTTCTTTTTCCCCC
4?			GCCACTTGTTGAACACTTACC	CATGTTATTGCTTCTTTTTCCCCC
5	-218/ exon5 /+194	553	TCTCCTTCCCTTTCCTTTTTACGC	GGAAATGAGGACTCATTGCAGGAC
6	-278/ exon6 /+94	502	CCATATTTAACATGGCAGACTTGAGGAC	GACATTATGCCTTTGGAGTGGGTAG
7	-195/ exon7 /+235	550	CAGAGCATCCCCATTGCTAGACTACTG	AAGCGTAAGTATCGCTTCCTCTATGCC
8	-76/ 501 exon8 /	577	TTCCCCTTCTAGGGATTTCAGCAC	TCCTCACGCTTAGTAACATAGCAAG
8.3	49579-51263	1684	AAAATGAAAAACACACGGCCATGA	CCACGCTGGGAAATGAAGAAGA
8.17	52232-53728	1496	GCACTAATCCAGATGCCTATTGTTGG	GCCACACTTTAATTCAATTGGAAAGG
8.18	53410-54908	1498	GAGATGGACTGTGGGTACTGGGAGT	AGGTAGCTCCAAAAAGGGAAGGGAGT
8.25	51167-52387	1220	AGCTACCTAGGAACATTCCTTGCAGACC	TCCAACAATAGGCATCTGGATTAGTGCT

FIGURE 2d

Sequencing Primers (Unless indicated, PCR primers were used as sequencing primers)

Exon	Primer Name	
Exon 1A	M13f	TGTAAAACGACGGCCAGT
Exon 1A	M13r	CAGGAAACAGCTATGACC
Exon 1A	ER1sq1Af.2	CTCCAGCACCTTTGTAAT
Exon 1G	ER1Gsf1_18720	CAGTATTGGCCAACATTTTC
Exon 1G	ER1Gsr1_19198	TGGTATCACCTTTTGAGACA
Exon 8.3	E1.8_49979	AAAGTATTACATCACGGGGG
Exon 8.3	E1.8_50379	TGGAGAGTAGACATTTTGCC
Exon 8.3	E1.8_50806	AGGGATAAGTTCCTGATTTTTG
Exon 8.17	ER1x8.17sf1_52232	GCACTAATCCAGATGCCTAT
Exon 8.17	ER1x8.17sf2_52684	TTGGTATTGGGTGTAGGAAC
Exon 8.17	ER1x8.17sf3_53160	GGAAGTGCAGTCTTTGATTT
Exon 8.17	ER1x8.17sr1_53702	AAATGCAGTTGGAAACAGAG
Exon 8.17	ER1x8.17sr2_53258	AAGTCCCTTATTTGTTCAGC
Exon 8.17	ER1x8.17sr3_52784	CCCCAGATAAATCACATCTT
Exon 8.18	ER1x8.18sf1_43410	GAGATGGACTGTGGGTACTG
Exon 8.18	ER1x8.18sf2_54033	GCCAGTTTCTGTTCTCTCAC
Exon 8.18	ER1x8.18sf3_54443	CTAAAGCCTCTCCTCACCTC
Exon 8.18	ER1x8.18sr1_54906	GTAGCTCCAAAAAGGGAAG
Exon 8.18	ER1x8.18sr2_54379	ACTGCTAGCAAGAAGTGGAG
Exon 8.18	ER1x8.18sr3_54048	GAGAACAGAAACTGGCATAA
Exon 8.25	ER1x8.25sf1_51173	CTAGGAACATTCCTTGCAGA
Exon 8.25	ER1x8.25sf3_51929	CTGTTTGTTTAAGAAGCACCT
Exon 8.25	ER1x8.25sr2_51945	GCTTCTTAAACAAACAGCAAC
Exon 8.25	ER1x8.25sr3_51565	TGGAATGAGCCTTTCTTTT
Exon 8.25	ER1x8.23r_52258	TCCAACAATAGGCATCTGGATTAGTGCT
Exon 8.25	ER1x8.25sf4_51860	CACTTAAATTTGGGGACAAT
Exon 8.25	ER1x8.25sr4_52072	GCATGTTAACCCAGTCAAAT

(SEQ ID NO:2)
Figure 3: Amino Acid Sequence for the Estrogen Receptor Alpha

```
1   mtmtlhtkas gmallhqiqg neleplnrpq lkiplerplg evyldsskpa vynypegaay
61  efnaaaaana qvygqtglpy gpgseaaafg snglggfppl nsvspsplml lhpppqlspf
121 lqphgqqvpy ylenepsgyt vreagppafy rpnsdnrrqg grerlastnd kgsmamesak
181 etrycavcnd yasgyhygvw scegckaffk rsiqghndym cpatnqctid knrrkscqac
241 rlrkcyevgm mkggirkdrr ggrmlkhkrq rddgegrgev gsagdmraan lwpsplmikr
301 skknslalsl tadqmvsall daeppilyse ydptrpfsea smmglltnla drelvhminw
361 akrvpgfvdl tlhdqvhlle cawleilmig lvwrsmehpv kllfapnlll drnqgkcveg
421 mveifdmlla tssrfrmmnl qgeefvclks iillnsgvyt flsstlksle ekdhihrvld
481 kitdtlihlm akagltlqqq hqrlaqllli lshirhmsnk gmehlysmkc knvvplydll
541 lemldahrlh aptsrggasv eetdqshlat agstsshslq kyyitgeaeg fpatv
```

FIGURE 3

Haplotype analysis of Estrogen receptor alpha.

Liverpool samples are from 48 patients, and each patient had a tumor and blood sample typed. Coriell samples were controls, but they were not matched controls. Rather they included a mix of Europeans, Chinese, Indo-Pakistani, and African Americans.

```
TITLE: ESR1 data from Coriell controls
#1-4
CGCAGCACTCTCGCATNNNNTGAACACAGTAACGTCGCTTCGTTACCGACCA
#2-12
CGTAGCACTCNCGCATTCGCTGAGCACAGTAACGTCGCTTCGTTGNCGACCA
#3
AGTAGCACTCNCGCATTCGCTGAGCACAGTAACGTCGCTTCGTTGNCGACCA
#4-4
CGTAGCACTCCCGCATTCGGTGAGCACAGTAACGCCGCTTCGTTGCCGACCA
#5-3
CGTAGCACTCCCGCATTCGGTGAGCACAGTAACGCCGCTTCGTTGCCGAGCA
#6-2
CGTAGCACTCCCGCATTCGGTGAGCACAGTAACGTCGATTCGATGANGACCA
#7
CGTAGCACTCCCGCATTCGGTGAGCACAATAACGTCGATTCGATGANGACCA
#8-3
CGTAGCACGCNCGCATTCGCTGAGCACAGTAACGTCGCTTCGTTGNCGANCA
#9
CGTAGGACGCTCGCATCCNNTGAGCACAGTAACGCCGCTTCGTTNNNNNNNN
#10-4
CGCAGCACTCNCGCATCCNNTGAGCACAGTAACGTCGCTTCGTTACCGACCA
#11
CGTAGCACTCNCGCATTCNNCTGACGCAGTAACGTCGCTTCGTTGCCGACCA
#12-2
CGTAGCANTCNCGCATCCGCTTAACGCAGTAACGCCGCTTCGTTGNNGAGCA
#13
CGCAGCACGCCCGCATTCGGTGAACACAGTAACGCCGATTCGATGACGAGCA
#14
CGTAGCACTCCCGCATTCNNTGAACACAATACCGCCGCGTCGTTGNCGAGCA
#15
CGTAGCACTCCNNCATTCNCTGAGCACAGTAACGTCGAGTCGATGCCGAGCG
#16
CGTAGCANNNCCGCATTCGCTGAGCACAATAACGCCGATTCGATGANGACCA
#17
CGTAGGACTCCCGCATTCGCTGAGCACAGTAACGTCGATTCGATGANGAGCA
#18
CGTAGCACTCCCGCATCCNNTGAGCACAATAACGCCGATTCGATGANGANNN
#19-8
CGTAGCACTCNCGCATNNNNNNNNNNCAATAACGCCGCTTCGTTGCNNNNNN
#20-6
CGCAGCACGCNCGCATNNNNNNNNNNCAGTAACGCCGCTTCGTTGCNNNNNN
#21
CGTAGCACTCNCGCATCCNNTTAGCGCAATAACGCCGCTTCGTTGCNGGCCA
#22
CGCAGCACTCCCGCATTCGCTTGGCGNNGNNNCGCCGCTTCGTTGCCGACCA
#23
CGCAGCACGCCCGCATCCNNTGAACATAATAACGCCGCTTCGTTGCCGAGCA
#24
CGCAGCACGCCCGTATTCNNTGAGCACAATAACGCCGCTTCGTTGNCGAGCA
#25
CGCAGCANNNCCGCATCCNNTGAACACAGTAACGCCGCTTCGTTGCCGAGCA
#26
CGCAGCACGCTCGCATCCNNTGAGCACAGTAACGTCGCTTCGATGANGANNN
#27
CGCAGCACTCCNNCATTCNNTTAACGCAGTACCGTTGCTTNGTTNNCGAGCN
#28
CGCACCACTCCCGCATTCNCTTGACGCAGTACCGTCAATTNGTTGCCGAGCA
#29
```

FIGURE 4a, sheet 1 of 6

CGCACCACGCCCGCATCCGCTGAACACAGTAACGTCGCTTCGTTNNNNNNNN
#30
CGTAGCACTCTCGCATCTGCTNAGCGCAGTAACGTCGCTTCGTTGCCGACCA
#31
CGCAGCACTCCCGCATNCNNTGAGCACAGTAACGCCGCTTCGTTGCGGAGCA
#32
CGCAGCACTCCCGCATTCGCTGAGCACAATAACGCCGCTTCGTTGCCGACCA
#33
CGCACCANNNCCGCATCCGCTGAGCANNGNNNCGTCGCTTCGTTGCCGAGCA
#34-2
CGCAGCACTCTCGCATCCGCTGAGCACAGTAACGCCGCTTCGTTGCCGAGCA
#35
CGTAGCACTCCCGCATCCNNTTGGCGCAGTAACGTCGATTCGACGACGAGCA
#36-3
CGTAGCACTCCCGCATTCGCTGAACACAGTAACGCCGCTTCGTTGNCGACCA
#37
CGCAGCACGCCCGCATTCNCTGAACACAGTAACGCCGCTTCGTTGCCGACCA
#38
CGCAGCACGCCCGCATTCNNTGAACACAATAACGCCGCTTCGTTGCNNNNNN
#39
CGCAGGACGCCCGCATTCGCTGAGCACAGTAACGCCGCTTCGTTGCNAAGCA
#40
CGCAGCACTCCCGCATTCNNTGAACACAATAACGTCGCTTCGTTACCGAGCA
#41
CGCAGCACTCNCGCATTCGCTGAACACAGTAACGTCGCTTCGTTGCNGAGCA
#42
CGCAGCACTCCCGCATTCNNTNGGCGCAATAACGTCGCTTNGTTGCCGACCA
#43
NNNNNGACTCCTGCATTCGCTTGGCGNNGNNNCGTTGCTTCGTTNNCGAGCA
#44
CGTAGCACTCNCGCATTCNCTTAGCGCAGTAACGTCGCTTCGTTGCCGGCTA
#45
CGCAGCACTCCCTCATTCNNTGAGCACAGTAACGCCGCTTCGTTGCCGACCA
#46
CGCAGCACTCTCGCATTCGCTGAACACAGTAACGTCGCTTCGTTGCCGAGCA
#47
CGTAGCACTCCCGCATTCGCTGAGCACAGTAACGCCGCTTCGTTGCCGAGCA
#48
CGCAGCACTCCCGCATTCGGTGAGCACNGTAACGTCGATTCGATGACGACCA
#49
CGCAGCACGCCCGCATTTGGTGAGCACNGTAACGTCGCTTCGTTACCGACCA
#50
CGCAGCACTCCCGCATCCNNTGAGCANNGTAACGTCGCTTCGTTGCCGACCA
#51
CGCAGCACTCCCGCATCCNNTGAGCANNGTAACGCCGCTTCGTTGCCGAGCA
#52
CGCAGGACGCCNNCATTCGCTGAGCACAGTAACGCCGCTTCGTTGCCGACCA
#53
CGCAGGACGCCNNCATTCGCTGAGCACAATAACGTCGCTTCGTTGCCGAGCA

FIGURE 4a, sheet 2 of 6

TITLE: ESR1LVR data - tumors in Liverpool

#1-6
CGCAGCACTCTCGCATCCGCTGAACATGGTAACGCCGCTTCGTTGC
#2-7
CGCAGCACTCTCGCATCCGCTGAACACGGTAACGTCGCTTCGTTGC
#3-31
CGTAGCACTCCCGCATCCGCTGAGCACGGTAACGTCGCTTCGTNNN
#4-7
CGCAGCACTCTCGCATCCGCTGAACACGGTAACGTCGCTTCGTTAC
#5-2
CGCAGCACTCTNNCATTCGGTGAGCACGGTAACGTCGCTTCGTTGC
#6
CGCAGCACTCTNNCATTCGGTGAGGACGGTAACGTCGCTTCGTTGC
#7-2
CGCAGCACTCTCGCATTCGCTGAACACGGTAACGTCGATTCGTTGC
#8
CGCAGCACTCTCGCATTCGCTGAACACGGTAACGTCGATTCGTTAC
#9-5
NGTAGCACTCTCGCATCCGCTGAACANNGNAACNNNNNNNNNNNNN
#10-2
NNCAGCACTCCCGCATTCGGTGAGCACGATAACGCCGCTTCGTTGC
#11
NNTANCACTCTNNCATCCGCTGAGCANNATAACGTCGCTTCGTTNN
#12-5
CGTAGCACTCTCGCATCCGCTGAGCANNGTAACGNCGCTNNNNNNN
#13
CGCAGCACTCCCGCATTCGCTGAGCACGACAAGGCCGCTTCGTTGC
#14-3
CGTAGCACTCTCGCATCCGCTGAGCACGATAACGCCGCTTCGTTGC
#15
CGCAGCACTCCNNCATTCGCTGAGCACGACAAGGCCGCTTCGTTGC
#16
CGTAGCACTCCCGCATCCGCTGAACACGGTAACGCCGCTTCGTTAC
#17
CGCAGCACGCTCGCACTCGCTGAACACGGTAACGCCGCTCCGATGC
#18
CGCAGCACTCTNNCATTCAGTTGGCGCGGTAACGCCGATTCGATGA
#19
CGCACCACGCCCGCATTCGCTGAAGACGGTAACGCCGCTTCGTTAC
#20-7
CGCAGCACTCCCGCATCCGCTGAGCACGGTAACGTCGCTTCGTTAC
#21
CGTAGCACTCCCGCATTCGCTTGGCGCGANNNCGCCGCTTCGTTGC
#22
NNNANCACTCTCGCATCCGCNGAGCACGGTAACGTCGATNNGATAA
#23
CGTAGCACTCTCGCATCCGCTGAGCACGATAACGCCGCTCCGTTGC
#24-2
CGTAGCACTCCNNCATTCGCTGAACACGATAACGNCGCTTCGTTAN
#25
CGCAGCACTCTCGCATCCGCTGAGCACGATAACGCCNCTCCGATGC
#26
CGCAGCACTCCCGCATTCGGTGAGCACGGTAACGTCGATTCGTTAC
#27
CGCAGCACTCCCGCATCCGCTGAACATGGTGACGCCGCTTCGTTAN
#28-5
CGCAGCACTCCCGCATTCGCTGAACACGGTAACGTCGCTTCGTTNN
#29
CGCAGCACTCTCGCATTCGGTGAACACGGTAACGTCGCTTCGTTAC
#30
CGCAGCACTCTCGCATTCAGTTGGCGCGGTAACGCCNCNTCGATGA
#31
NNNNNCACGCCCGCATTCGCTGAAGACGGTAACGCCGCTTCGTTAC
#32
CGCAGCACTCCCGCATTCGGTTGGCGCGGTAACGTCGCTCCGATAC

FIGURE 4a, sheet 3 of 6

#33
CGTAGCACTCCCGCATTCGCTTGGCGCGATAACGCCGCTTCGTTGC
#34
NNNAGCACTCTNNCATTCGCTGAGCANNGNNNNNNCGATNNGTNNN
#35
CGTAGCACTCTCGCATCCGCTGAGCACGATAACGCCGCTCCGATGC
#36
CGTAGCACTCCCGCATTCGCTGAACACGATAACGCCGCTTCGTTAC
#37
CGCAGCACTCTCGCATCCGGTGAGCACGATAACGTCGCTCCGATGC
#38
CGCAGCACTCCCGCATTCGGTGAGCACGGTAACGTCGATTCGATAA
#39
CGCAGCACTCCCGCATCCGCTGAACATGGTGACGCCGCTTCGTTGC
#40
CGTACCACGCCCGCATCCGCTGAGCACGATAACGCCNCNNCGTNNN
#41
CGCAGCACTCCCGCATTCGCTGAACACGGTAACGTCGCTTCGTTAC
#42
CGTAGCACGCTCGCATCCGCTGAGCACGATAACGCCGCTTCGTTGC
#43
CGTAGCACTCTCGCATCCGCTGAGCACGGTAACGTCGCTTCGTTAC
#44
CGTAGCACTCCCGCATTCGGTGAGGACGATAACGCCGCTTCGTTGC
#45-2
CGTAGCACTCCCGCATTCGCTGAACACGGTAACGTCGCTTCGATAA
#46-5
CGCAGCACTCCCGCATCCGCTGAACACGGTAACGCCGCTTCGTTGN
#47-3
CGTAGCACTCCCGCATCCGCTGAACACGATAACGCCGCTTCGTTGC
#48
CGCACCACGCCCGCATTCGCTGAGCACGGTAACGCCGCTTCGTTGC
#49
CGTAGCACTCCCGCATCCGCTGAGCACGATAACGCCGCTTCGTTGC
#50-3
NNNNNCACTCCCGCATTCGCTGAGCANNGTAACGCCGCTNNGTNNN
#51
CGCAGCACTCCNNCATTCGGTGAGCACGGTAAGGCCGCTTCGTTGC
#52
CGCACCACGCCCGCATCCGCTGAGCACGGTAACACCGCTNNGTTGN
#53-5
CGCACCACGCCCGCATCCGCTGAGCANNGTAACGCCGCTTCGTTNN
#54
CGCAGCACTCCNNCATTCGGTGAGCACGGTAAGGCCGCTTCGTTNN
#55
CGTAGCACTCCCGCATTCGCTGAACACGATAACGCCGCTNNGTTGC
#56
CGCACCACGCCCGCATCCGCTGAGCACGATAACGCCGCTTCGTTGC
#57-2
CGCACCACGCTNNCATCCNNTGAGCACGGTAACGTCGCTTCGTTGC
#58
CGCACCACGCTCGCATCCGCTGAGCACGGTAACGTCGCTTCGTTGC
#59
CGCAGCACTCTCTCATTCGCTGAGCANNATAACACCGCTTCGTTGC
#60
CGCAGCACGGTCGCATTCGCTGAGCACAATAACGCCGCTTCGTTGC
#61-3
NGTAGCACTCCNNCATTCGGTTGGCGNNGTAACGCCGCTTCGTTNN
#62
CGCAGCACGGTNNCATTCGCTGAGCACGATAACGCCGCNTCGTTGC
#63
CGTAGCACTCCNNCATTCGGTTGGCGCGGNNNCGCCGCTTCGTTAC
#64
CGTAGCACTCTNNCATTCGCTGGGCGCGGTAACGTCNCTNNGTTNN
#65

FIGURE 4a, sheet 4 of 6

CGTAGCACTCCCGCATTTGCTGAGCACGGTAACGCNGCTCCGATGC
#66
CGCACCAGGCTCGCATTCGCTTAGCGCGGTAACGCCGCTTCGTTGC
#67
CGTAGCACTCCCGCATTTGGTGAGCACGGTAACGCCGCTCCGATGC
#68
CGCACCAGGCTCGCATTCGCTTAGCGCGGTAACGCCGCTTCGTTAC
#69
CGTAGCACTCCCGCATTCGCTGAGCACGATAACGCCGCTTCGTTGC
#70
CGTAGCACGCCNNCATTCGCTGAGCACGGTAACGCCGCTTCGTTGC
#71
CGTAGCACTCCCGCATCTGGTGAGCACGGTAACGCCGCTTCGTTGC
#72
CGTAGCACTCCCGCATTCGGTGAGCACGATAACGCCGCTTCGTTGN
#73-2
CGCGCCAGGCTCGCATCCGCTTAACGCGGTAACGTCGCTTCGTTAC
#74
CGCACCACGCCNNCATCCGCTGAGCACGATAACGTCGCTTCATTGN
#75
CGCACCACGCCCGCATCCGCTGAGCACGATAACGTCGCTTCATTGC
#76-2
CGCAGCACGCCCGCATCCGCTGAGCACGGTAACGTCGCTTCATTGC
#77-2
CGCAGCACTCCCGCATTCGCTTGGCGCGGTAACGTCGCTTTGTTAC
#78
CGCAGCACGCTCGCATCCGCTGAGCACGGTAACGTCNCTTCGTTGC
#79
CGCAGCACTCTCGCATCCGCTGAGCACGGTAACGTCGCTNNGTTGC
#80
CGCAGCACTCTCGCATCCGCTGAGCACGGTAAGGCCGCTNNGTTAC
#81
CGCAGCACTCTCGCATCCGCTGAGCACGGTAACGTCGCTTCGTTGC
#82
CGCAGCACTCTCGCATCCGCTGAGCACGGTAAGGCCGCTTCGTTAC
#83
CGTAGCACTCCCGCATTCGCTGAGCACGGTAACGTCGCTTCGTTGC
#84
CGTAGCACTCTCGCATTCGCTGAACACGGTAACGTCGCTCCGTTAC
#85
CGTAGCACTCCCGCATCCGCTGGGCACGGTAACGTCGCTTCGTTGC
#86
CGTAGCACTCCCGCATTCGGTTGGCGCGGTAACGTCGCTTCGTTAC
#87
CGTAGCACTCCNNCATCCGCTGGGCACGGTAACGTCGCTTCGTTGC
#88
CGCAGCACTCCNNCATTCGGTTGGCGCGGTAACGTCGCTTCGTTAC
#89
CGCAGCACTCCCGCATTCGGTGAGCACGGTAACGCCGCTTCGTTGC
#90
CTTAGCACTCCCGCATTCGGTGAGCACGGTAACGCCGCTTCGTTGC
#91
CGCAGCACTCCCGCATTCGGTGAGCACGGTAACGCCGCTTCGTTGC
#92
CTTAGCACTCCCGCATTCGGTGAGCACGGTAACGCCGCTTCGTTGC
#93
CGTAGCACTCCCGCATTCGCTTGGCGCGGTAACGCCGCTTCGTTGC
#94
CGCAGGGCGCCCGCATTCGCTTAGCGCGGTAACGCCGCTTCGTTGC
#95
CGTAGCACTCCNNCATTCGCTTGGCGCGGTAACGCCGCTTCGTTGN
#96
CGCAGGGCGCCNNCATTCGCTTAGCGCGGTAACGCCGCTTCGTTGN
#97
CGTAGCACTCCNNCATTCGGTGAGCACGGTAACGCCGCTTCGTTGC

FIGURE 4a, sheet 5 of 6

#98
CGTAGCACTCTNNCATTTGGTGAGCACGGTAACGCCGCTTCGTTGC
#99
CGTAGCACTCCCGCATTCGGTGAGCACGGTAACGCCGCTTCGTTGC
#100
CGTAGCACTCTCTCATTTGGTGAGCACGGTAACGCCGCTTCGTTGC
#101
CGTAGCACTCCNNCATTCGGTTGGCGCGGTAACGTCGCTTCGTTAC
#102
CGCAGCACGCCNNCATCCGCTTGGCACGGTAACGTCGCTTCGTTAC

FIGURE 4a, sheet 6 of 6

The non-singleton haplotype data were fitted to a neighbor-joining tree (L is Liverpool sample):

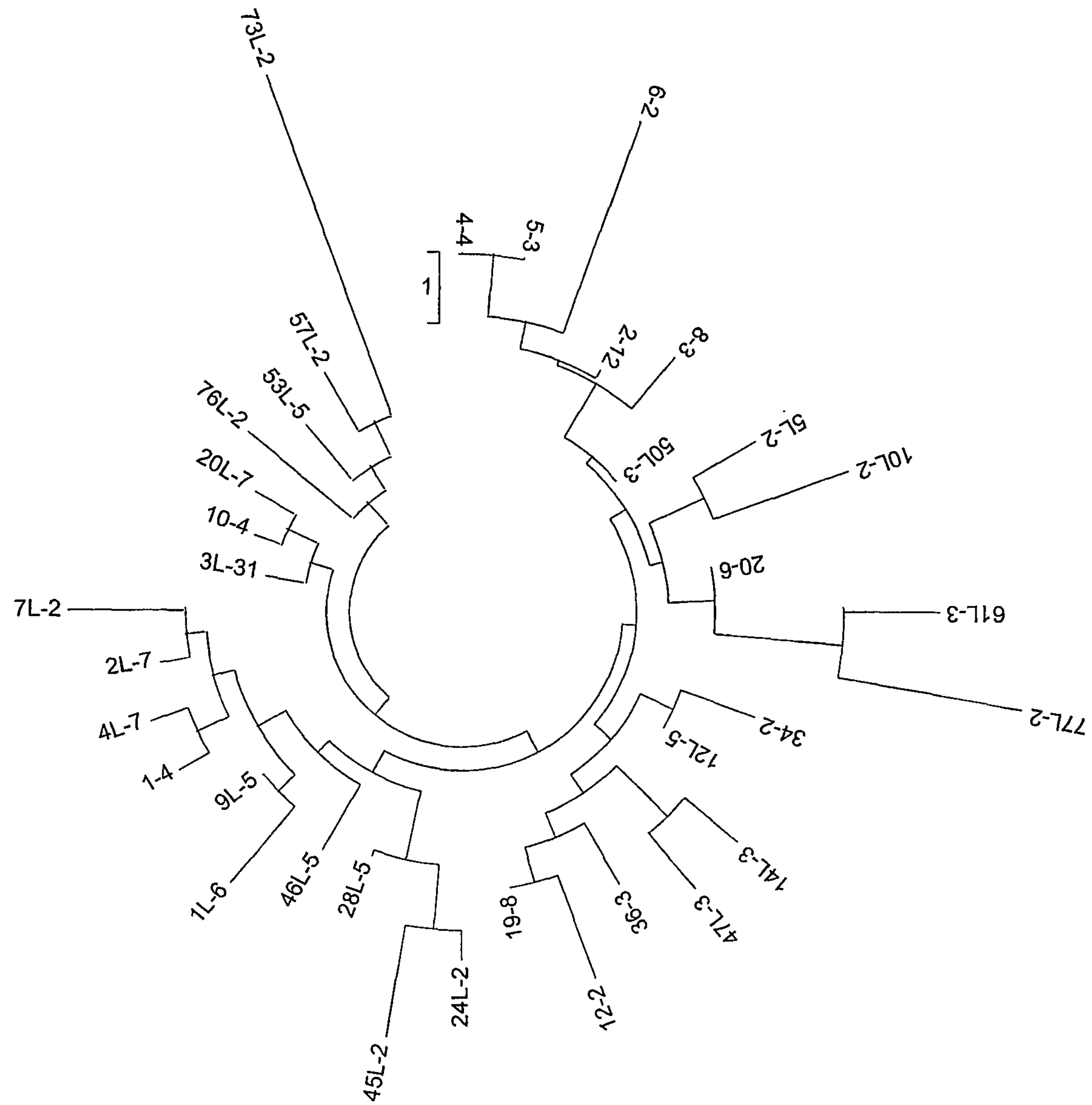


FIGURE 4b

A reconstructed haplotypes cladogram which indicated a subset of SNPs in ER1 that preserve the property of having clades highly enriched in the tumor samples or the control.

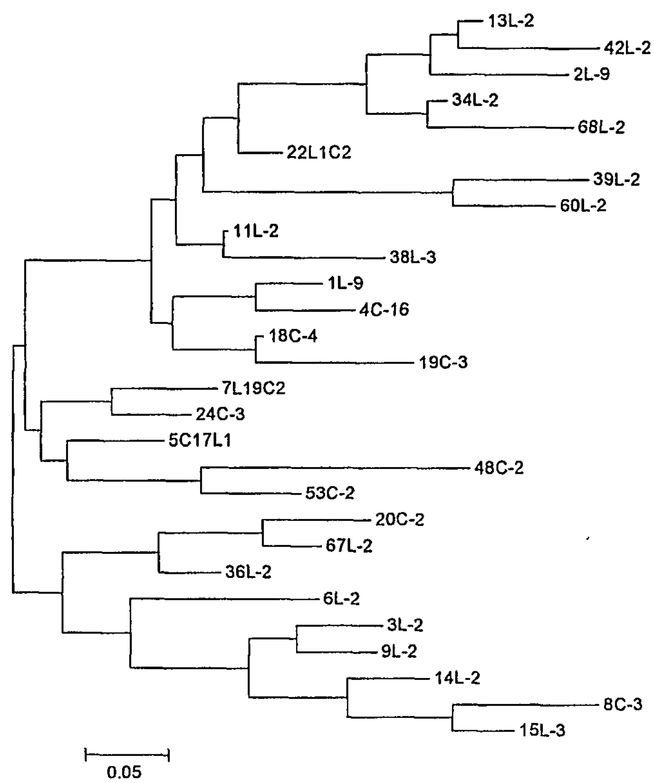
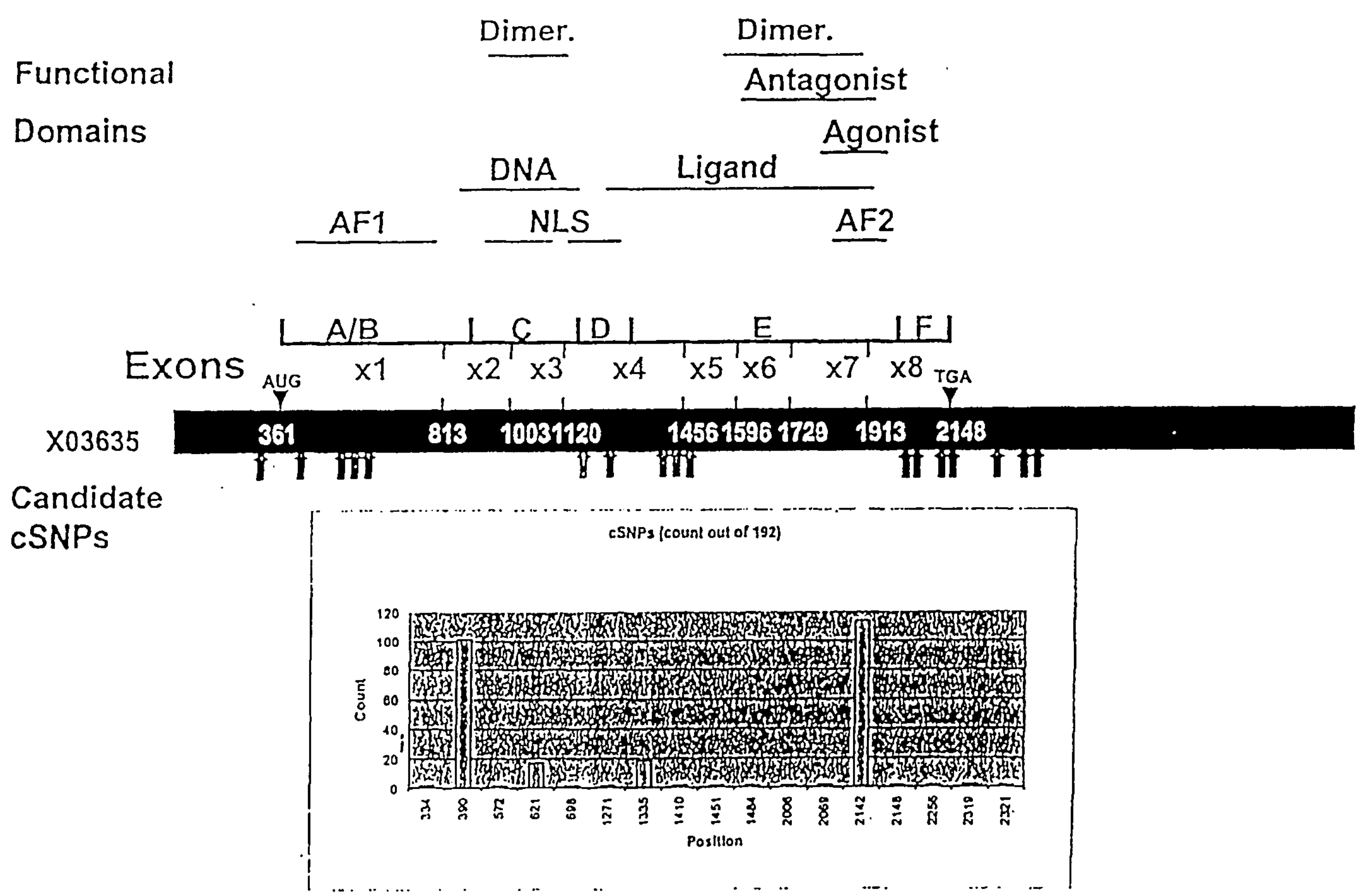


FIGURE 4c

FIGURE 5

cSNP candidates



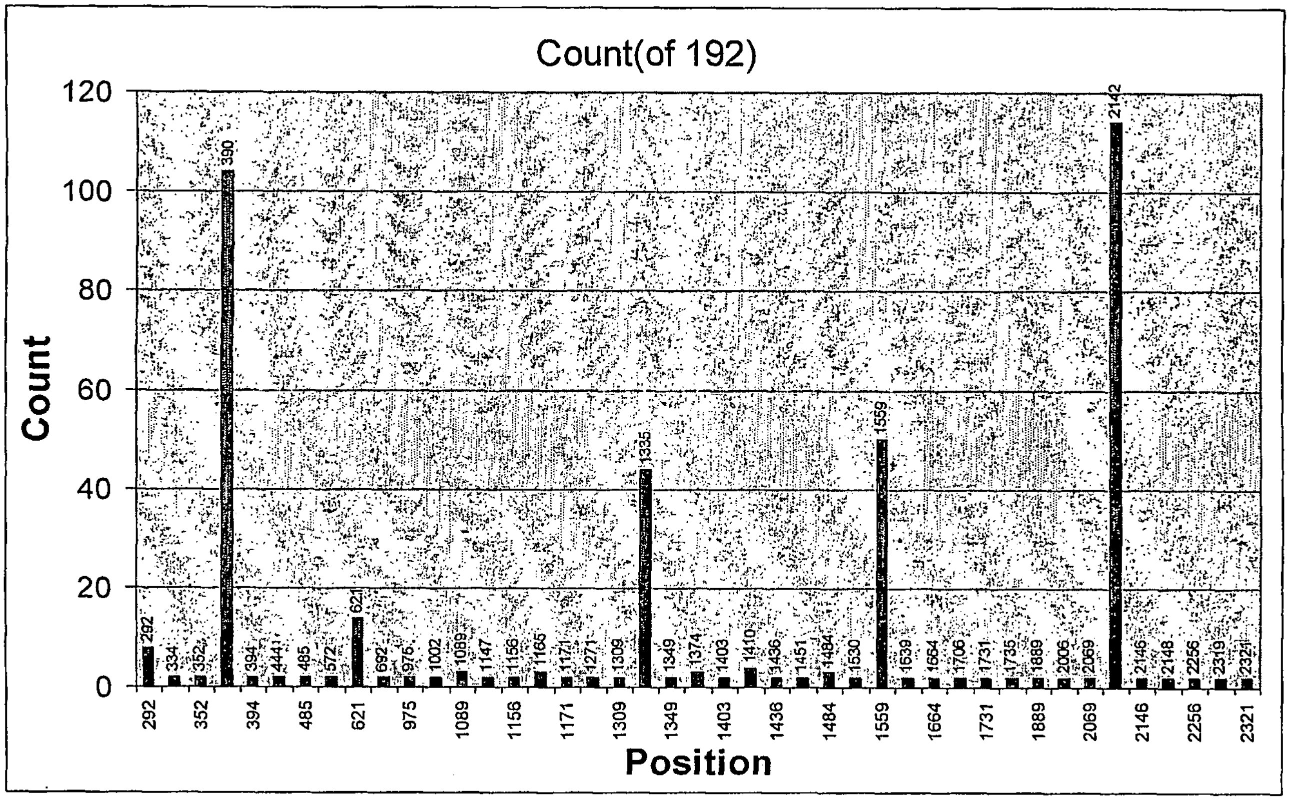
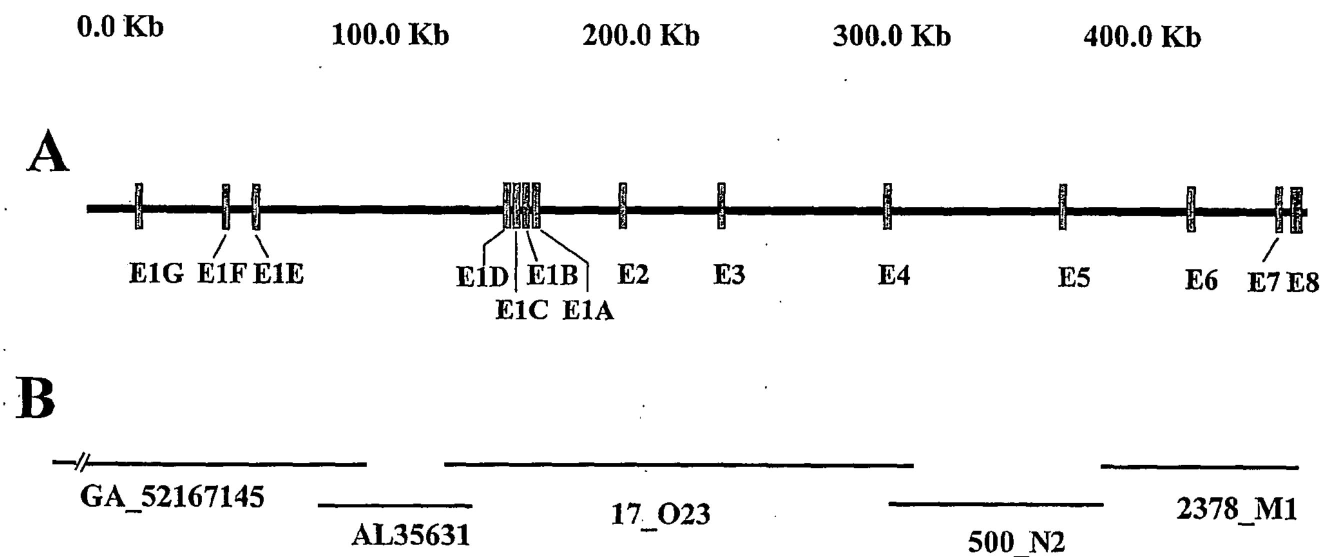

Count(of 192)
Count
Position
0
20
40
60
80
100
120
292
352
394
485
621
975
1089
1156
1171
1309
1349
1403
1436
1484
1559
1664
1731
1889
2069
2146
2256
2321

FIGURE 6

Estrogen Receptor Alpha



(A) Complete structure of the human estrogen receptor alpha (ERα). Exons are represented by filled boxes and introns by horizontal lines. (B) Order and names of contigs used to complete the genomic sequence. GA numbers represent Celera contig numbers. Research genetics BAC clones are represented by standard plate and well numbering.

FIGURE 7

		1A 170035		1A 170068		1A 170256		1A 170368		1A 170487		1B 169812		1B 169823		1C 167950	
		C	A	G	T	C	T	A	G	G	C	C	G	A	G	C	G
total	total	0.99	0.01	1	0	0.46	0.54	1	0	0.96	0.04	0.94	0.06	1	0	1	0
N. Eur	N. Eur	1	0	1	0	0.55	0.45	1	0	0.9	0.1	1	0	1	0	1	0
a01	GM03715	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a02	GM06816	2	0	2	0	1	1	2	0	1	1	2	0	2	0	n/a	n/a
a03	GM10923	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
a04	GM10924	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a05	GM11814	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a06	GM12136	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
a07	GM12137	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
a08	GM12547	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
a09	GM12548	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
a10	GM14667	2	0	2	0	0	2	2	0	2	0	2	0	2	0	n/a	n/a
Chi	Chi	0.95	0.05	1	0	0.5	0.5	1	0	0.95	0.05	1	0	1	0	1	0
b01	GM00576	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b02	GM03433	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b03	GM06090	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
b04	GM07426	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
b05	GM09820	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
b06	GM11321	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
b07	GM11322	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b08	GM11323	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
b09	GM11324	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0
b10	GM11325	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
In. Pak	In. Pak	1	0	1	0	0.5	0.5	1	0	1	0	1	0	1	0	1	0
c01	GM01032	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
c02	GM01225	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
c03	GM04300	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
c04	GM07895	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
c05	GM10176	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
c06	GM10666	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
c07	GM10667	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
c08	GM11213	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
c09	GM11860	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c10	GM14611	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
Af. Amer	Af. Amer	1	0	1	0	0.5	0.5	1	0	0.94	0.06	0.9	0.1	1	0	1	0
d01	GM14660	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1	1	2	0	2	0
d02	GM14661	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d03	GM14663	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
d04	GM14665	2	0	2	0	1	1	2	0	2	0	1	1	2	0	2	0
d05	GM14672	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
d06	GM14682	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
d07	GM14683	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
d08	GM14696	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
d09	GM14698	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
d10	GM14700	2	0	2	0	1	1	2	0	2	0	2	0	2	0	n/a	n/a
SW Amer. Ind	SW Amer. Ind	1	0	1	0	0.25	0.75	1	0	1	0	0.8	0.2	1	0	1	0
e01	GM12060	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
e02	GM12061	2	0	2	0	1	1	2	0	2	0	1	1	2	0	2	0
e03	GM12062	2	0	2	0	0	2	2	0	2	0	2	0	2	0	n/a	n/a
e04	GM12063	2	0	2	0	0	2	2	0	2	0	1	1	2	0	2	0
e05	GM12064	2	0	2	0	2	0	2	0	2	0	0	2	2	0	2	0
e06	GM14308	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
e07	GM14309	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
e08	GM12310	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
e09	GM14311	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
e10	GM14313	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0

FIGURE 8a, sheet 1 of 6

	1C 167989		1C 168054		1E 64331		1F 52901		1F 52877		1G 18783		1G 18937		1G 19034		Intron 3 243187	
	T	G	C	G	T	C	C	T	G	T	C	T	A	C	T	C	C	T
total	0.76	0.24	1	0	0.2	0.8	0.99	0.01	0.99	0.01	0.99	0.01	0.99	0.01	1	0	0.33	0.674
N. Eur	0.94	0.06	1	0	0.45	0.55	1	0	0.95	0.05	1	0	1	0	1	0	0.67	0.333
a01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	n/a	n/a
a02	n/a	n/a	n/a	n/a	0	2	2	0	2	0	2	0	2	0	2	0	2	0
a03	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a04	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0	1	1
a05	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
a06	2	0	2	0	n/a	1	2	0	2	0	2	0	2	0	2	0	1	1
a07	2	0	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	0	2
a08	1	1	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
a09	2	0	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	1	1
a10	2	0	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	1	1
Chi	0.75	0.25	1	0	0	1	1	0	1	0	1	0	0.95	0.05	1	0	0.3	0.7
b01	1	1	2	0	0	2	2	0	2	0	2	0	1	1	2	0	0	2
b02	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
b03	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
b04	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
b05	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
b06	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
b07	1	1	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	0	2
b08	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
b09	2	0	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	0	2
b10	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
In. Pak	0.75	0.25	1	0	0.28	0.72	1	0	1	0	1	0	1	0	1	0	0.25	0.75
c01	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
c02	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
c03	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
c04	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
c05	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
c06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c07	1	1	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	1	1
c08	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	1	1
c09	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
c10	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
Af. Amer	0.61	0.39	1	0	0.22	0.78	0.94	0.06	1	0	0.95	0.05	1	0	1	0	0.28	0.722
d01	1	1	2	0	0	2	1	1	2	0	2	0	2	0	2	0	1	1
d02	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	n/a	n/a
d03	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
d04	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d05	1	1	2	0	0	2	2	0	2	0	1	1	2	0	2	0	0	2
d06	1	1	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	1	1
d07	1	1	2	0	0	2	n/a	n/a	n/a	n/a	2	0	2	0	2	0	0	2
d08	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
d09	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
d10	n/a	n/a	n/a	n/a	0	2	2	0	2	0	2	0	2	0	2	0	1	1
SW Amer. Ind	0.72	0.28	1	0	0.13	0.88	1	0	1	0	1	0	1	0	1	0	0.13	0.875
e01	2	0	2	0	0	2	n/a	n/a	n/a	n/a	2	0	2	0	2	0	0	2
e02	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
e03	n/a	n/a	n/a	n/a	0	2	2	0	2	0	2	0	2	0	2	0	0	2
e04	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
e05	0	2	2	0	0	2	n/a	n/a	n/a	n/a	2	0	2	0	2	0	0	2
e06	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	1	1
e07	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
e08	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
e09	2	0	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	n/a	n/a
e10	1	1	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	n/a	n/a

FIGURE 8a, sheet 2 of 6

	Exon 3 243055		Exon 4 306292		Exon 4 306382		Exon 6 423067		intron 6 423149		Intron 6 423163		Intron 6 423220		Intron 6 423232		Intron 6 423258	
	C	T	G	0	C	G	T	C	G	T	A	G	G	A	C	G	A	G
total	0.98	0.02	1	0	0.83	0.17	0.99	0.01	0.81	0.19	0.88	0.13	0.75	0.25	1	0	0.8	0.2
N. Eur	1	0	1	0	1	0	0.95	0.05	0.85	0.15	0.95	0.05	0.8	0.2	1	0	0.85	0.15
a01	n/a	n/a	n/a	n/a	n/a	n/a	2	0	2	0	2	0	0	2	2	0	2	0
a02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a03	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a04	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
a05	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
a06	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
a07	2	0	n/a	n/a	n/a	n/a	1	1	1	1	1	1	1	1	2	0	1	1
a08	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a09	2	0	n/a	n/a	n/a	n/a	2	0	1	1	2	0	2	0	2	0	1	1
a10	2	0	2	0	2	0	2	0	1	1	2	0	1	1	2	0	1	1
Chi	1	0	1	0	0.75	0.25	1	0	0.65	0.35	0.7	0.3	0.75	0.25	1	0	0.65	0.35
b01	2	0	2	0	0	2	2	0	0	2	0	2	2	0	2	0	0	2
b02	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	1	1	2	0	2	0
b03	2	0	2	0	1	1	2	0	2	0	2	0	1	1	2	0	2	0
b04	2	0	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
b05	2	0	n/a	n/a	n/a	n/a	2	0	0	2	0	2	2	0	2	0	0	2
b06	2	0	n/a	n/a	2	0	2	0	0	2	1	1	2	0	2	0	0	2
b07	2	0	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
b08	2	0	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
b09	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b10	2	0	2	0	1	1	2	0	1	1	1	1	2	0	2	0	1	1
In. Pak	0.9	0.1	1	0	0.75	0.25	1	0	0.89	0.11	0.9	0.1	0.6	0.4	1	0	0.85	0.15
c01	2	0	2	0	2	0	2	0	2	0	2	0	0	2	2	0	2	0
c02	2	0	2	0	2	0	2	0	1	1	2	0	1	1	2	0	1	1
c03	2	0	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
c04	2	0	n/a	n/a	2	0	2	0	2	0	2	0	0	2	2	0	2	0
c05	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
c06	1	1	2	0	2	0	2	0	n/a	1	2	0	2	0	2	0	1	1
c07	2	0	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
c08	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	1	1	2	0	2	0
c09	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
c10	2	0	n/a	n/a	n/a	n/a	2	0	1	n/a	0	2	2	0	2	0	1	1
Af. Amer	1	0	1	0	1	0	1	0	0.7	0.3	0.85	0.15	0.65	0.35	1	0	0.7	0.3
d01	2	0	2	0	2	0	2	0	0	2	0	2	2	0	2	0	0	2
d02	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
d03	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	1	1	2	0	2	0
d04	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	1	1	2	0	2	0
d05	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
d06	2	0	n/a	n/a	2	0	2	0	0	2	2	0	2	0	2	0	0	2
d07	2	0	n/a	n/a	n/a	n/a	2	0	1	1	2	0	1	1	2	0	1	1
d08	2	0	n/a	n/a	2	0	2	0	1	1	1	1	1	1	2	0	1	1
d09	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	0	2	2	0	2	0
d10	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	1	1	2	0	2	0
SW Amer. Ind	1	0	1	0	0.85	0.15	1	0	1	0	1	0	1	0	1	0	1	0
e01	2	0	1	n/a	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e03	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e05	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e06	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
e07	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
e08	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
e09	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
e10	n/a	n/a	1	n/a	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

FIGURE 8a, sheet 3 of 6

	8 208		8 220		Exon 8 460929		Exon 8 461199		Exon 8 461231		Exon 8 461337		Exon 8 461520		Exon 8 461843		Exon 8 461968	
	C	T	A	G	G	A	T	C	A	G	A	C	C	G	G	A	T	C
total	0.99	0.01	1	0	0.79	0.21	1	0	1	0	0.97	0.03	1	0	1	0	0.53	0.47
N. Eur	1	0	1	0	0.8	0.2	1	0	1	0	1	0	1	0	1	0	0.55	0.45
a01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a02	n/a	n/a	n/a	n/a	1	1	n/a	n/a	n/a	n/a	n/a	n/a	2	0	2	0	1	1
a03	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
a04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
a05	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0	1	1
a06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a08	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
a09	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
a10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
Chi	1	0	1	0	0.85	0.15	1	0	1	0	1	0	1	0	1	0	0.6	0.4
b01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b02	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
b03	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
b04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b05	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
b06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
b08	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
b09	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b10	n/a	n/a	n/a	n/a	2	0	n/a	n/a	n/a	n/a	n/a	n/a	2	0	2	0	0	2
In. Pak	0.95	0.05	1	0	0.8	0.2	1	0	1	0	1	0	1	0	1	0	0.4	0.6
c01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
c02	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
c03	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
c04	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
c05	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
c06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c08	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
c09	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c10	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
Af. Amer	1	0	1	0	0.8	0.2	1	0	1	0	0.83	0.17	1	0	1	0	0.45	0.55
d01	n/a	n/a	n/a	n/a	2	0	n/a	n/a	n/a	n/a	n/a	n/a	2	0	2	0	1	1
d02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
d03	2	0	2	0	1	1	2	0	2	0	1	1	2	0	2	0	1	1
d04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
d05	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
d06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
d07	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
d08	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
d09	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0	0	2
d10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
SW Amer. Ind	1	0	1	0	0.7	0.3	1	0	1	0	1	0	1	0	1	0	0.65	0.35
e01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e02	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	0	2
e03	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
e04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e05	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
e06	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
e07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e08	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
e09	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0	1	1
e10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1

FIGURE 8a, sheet 4 of 6

	Exon 8 462125		8 462398		8 462683		8 462949		8 463958		8 463966		8 464237		8 464735		8 465074	
	C	T	G	A	C	A	T	G	T	C	C	T	G	A	T	A	T	C
total	0.98	0.02	0.99	0.01	0.89	0.11	0.98	0.02	0.98	0.02	1	0	1	0	0.87	0.13	0.99	0.01
N. Eur	1	0	1	0	1	0	1	0	0.9	0.1	1	0	1	0	0.9	0.1	1	0
a01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a03	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a05	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a08	2	0	2	0	2	0	2	0	0	2	2	0	2	0	0	2	2	0
a09	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
Chi	1	0	1	0	0.9	0.1	1	0	1	0	1	0	1	0	0.9	0.1	0.95	0.05
b01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b03	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1	2	0
b04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b05	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1	1	1
b06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b08	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b09	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
In. Pak	1	0	1	0	0.95	0.05	1	0	1	0	1	0	1	0	0.95	0.05	1	0
c01	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c03	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c05	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c08	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c09	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1	2	0
c10	2	0	2	0	2	0	2	0	2	0	n/a	n/a	2	0	2	0	2	0
Af. Amer	0.9	0.1	0.95	0.05	0.95	0.05	0.95	0.05	1	0	1	0	1	0	1	0	1	0
d01	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d03	2	0	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
d04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d05	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d06	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d07	1	1	2	0	2	0	2	0	2	0	n/a	n/a	2	0	2	0	2	0
d08	2	0	1	1	1	1	2	0	2	0	n/a	n/a	2	0	2	0	2	0
d09	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
d10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
SW Amer. Ind	1	0	1	0	0.65	0.35	0.95	0.05	1	0	1	0	1	0	0.6	0.4	1	0
e01	2	0	2	0	1	1	1	1	2	0	2	0	2	0	1	1	2	0
e02	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e03	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1	2	0
e04	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1	2	0
e05	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e06	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1	2	0
e07	2	0	2	0	1	1	2	0	2	0	2	0	2	0	0	2	2	0
e08	2	0	2	0	0	2	2	0	2	0	2	0	2	0	0	2	2	0
e09	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
e10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0

FIGURE 8a, sheet 5 of 6

	3' Flanking Exon 8 (AL078582)															
	54404		54460		48798		48924		49005		49116		49148		49251	
	G	A	C	A	C	G	G	A	A	G	C	G	C	T	A	G
total	0.88	0.12	0.88	0.13	0.99	0.01	0.99	0.01	0.98	0.02	0.64	0.36	0.99	0.01	0.99	0.01
N. Eur	0.85	0.15	1	0	1	0	1	0	0.95	0.05	0.7	0.3	1	0	1	0
a01	0	2	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a02	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
a03	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
a04	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
a05	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
a06	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a07	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
a08	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
a09	2	0	2	0	n/a	n/a	2	0	1	1	2	0	2	0	2	0
a10	2	0	n/a	n/a	n/a	n/a	2	0	2	0	1	1	2	0	2	0
Chi	0.78	0.22	0.86	0.14	1	0	1	0	1	0	0.78	0.22	1	0	1	0
b01	0	2	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0
b02	1	1	2	0	2	0	2	0	2	0	1	1	2	0	2	0
b03	2	0	1	1	2	0	2	0	2	0	1	1	2	0	2	0
b04	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
b05	2	0	1	1	2	0	2	0	2	0	1	1	2	0	2	0
b06	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
b07	2	0	2	0	n/a	n/a	2	0	2	0	1	1	2	0	2	0
b08	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
b09	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0	2	0
b10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
In. Pak	0.85	0.15	0.94	0.06	1	0	1	0	1	0	0.72	0.28	1	0	1	0
c01	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
c02	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
c03	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
c04	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c05	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
c06	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
c07	1	1	n/a	n/a	2	0	2	0	2	0	n/a	n/a	2	0	2	0
c08	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
c09	1	1	1	1	2	0	2	0	2	0	2	0	2	0	2	0
c10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
Af. Amer	0.93	0.07	1	0	0.94	0.06	1	0	0.94	0.06	0.31	0.69	0.94	0.06	1	0
d01	n/a	n/a	n/a	n/a	2	0	2	0	2	0	1	1	2	0	2	0
d02	1	1	2	0	1	1	2	0	2	0	1	1	2	0	2	0
d03	2	0	n/a	n/a	2	0	2	0	2	0	1	1	2	0	2	0
d04	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
d05	2	0	n/a	n/a	2	0	2	0	2	0	0	2	2	0	2	0
d06	2	0	2	0	2	0	2	0	1	1	2	0	1	1	2	0
d07	n/a	n/a	n/a	n/a	2	0	2	0	2	0	0	2	2	0	n/a	n/a
d08	2	0	2	0	2	0	2	0	2	0	0	2	2	0	2	0
d09	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
d10	2	0	2	0	2	0	2	0	2	0	0	2	2	0	2	0
SW Amer. Ind	1	0	0.65	0.35	1	0	0.94	0.06	1	0	0.67	0.33	1	0	0.92	0.08
e01	2	0	2	0	2	0	2	0	2	0	1	1	2	0	1	1
e02	2	0	2	0	n/a	n/a	1	1	2	0	1	1	2	0	2	0
e03	2	0	1	1	n/a	n/a	2	0	2	0	2	0	2	0	2	0
e04	2	0	1	1	n/a	n/a	2	0	2	0	1	1	2	0	2	0
e05	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
e06	2	0	1	1	n/a	n/a	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a
e07	2	0	0	2	1	n/a	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a
e08	2	0	0	2	n/a	n/a	2	0	2	0	2	0	2	0	2	0
e09	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
e10	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

FIGURE 8a, sheet 6 of 6

	exon 1A 170035		exon 1A 170068		exon 1A 170256		exon 1A 170368		exon 1A 170487		exon 1B 169812		exon 1B 169823		exon 1C 167950	
	C	A	G	T	C	T	A	G	G	C	C	G	A	G	C	G
	1.00	0.00	0.99	0.01	0.55	0.45	0.99	0.01	0.87	0.13	0.99	0.01	0.99	0.01	0.98	0.02
T1	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T2	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T3	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T4	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T5	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T6	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T7	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
T8	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T9	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T10	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T11	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T12	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T13	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T14	2	0	2	0	1	1	2	0	2	0	1	1	1	1	2	0
T15	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T16	n/a	n/a	n/a	n/a	n/a	n/a	2	0	n/a	n/a	2	0	2	0	2	0
T17	2	0	1	1	1	1	2	0	2	0	2	0	2	0	2	0
T18	2	0	2	0	2	0	2	0	1	1	2	0	2	0	1	1
T19	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T20	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T21	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T22	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T23	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T24	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T25	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T26	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T27	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T28	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T30	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T31	2	0	2	0	2	0	1	1	0	2	2	0	2	0	1	1
T32	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T33	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T34	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T35	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
T36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T37	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T38	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
T39	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T40	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T41	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T42	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T43	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
T44	n/a	n/a	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T45	2	0	2	0	2	0	2	0	0	2	2	0	2	0	2	0
T46	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T47	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T48	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0

FIGURE 8b, sheet 1 of 12

	exon 1C 167989		exon 1C 168054		exon 1E 64331		exon 1F 52901		exon 1F 52877		exon 1G 18783		exon 1G 18937		exon 1G 19034	
	T	G	C	G	C	T	C	T	G	T	C	T	A	C	T	C
	0.83	0.17	0.99	0.01	0.63	0.38	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00
T1	2	0	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T2	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T3	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T4	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T5	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T6	2	0	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T7	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T8	0	2	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T9	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T11	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T12	1	1	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T13	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T14	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T15	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T16	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T17	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T18	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T19	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T20	2	0	2	0	0	2	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T21	2	0	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T22	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T23	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T24	2	0	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T25	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T26	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T27	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T28	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T29	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T30	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T31	0	2	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T32	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T33	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T34	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T35	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T36	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T37	1	1	1	1	1	1	2	0	2	0	2	0	2	0	2	0
T38	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T39	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T40	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T41	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T42	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T43	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T44	2	0	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T45	0	2	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
T46	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T47	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T48	1	1	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0

FIGURE 8b, sheet 2 of 12

	Intron 3 243187		exon 3 243055		exon 4 306292		exon 4 306382		exon 6 423067		Intron 6 423149		Intron 6 423163		Intron 6 423220	
	C	T	C	T	G	A	C	G	T	C	G	T	A	G	G	A
	0.63	0.38	0.97	0.03	0.99	0.01	0.83	0.17	1.00	0.00	0.88	0.13	0.90	0.10	0.70	0.30
T1	1	1	2	0	2	0	1	1	2	0	2	0	2	0	2	0
T2	1	1	1	1	2	0	1	1	2	0	2	0	2	0	2	0
T3	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T4	1	1	1	1	2	0	2	0	2	0	2	0	2	0	1	1
T5	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
T6	1	1	2	0	1	1	1	1	2	0	1	1	1	1	2	0
T7	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T8	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T9	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T11	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T12	1	1	2	0	2	0	1	1	2	0	0	2	0	2	2	0
T13	0	2	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T14	0	2	2	0	2	0	2	0	2	0	0	2	1	1	2	0
T15	1	1	2	0	2	0	2	0	2	0	1	1	1	1	2	0
T16	2	0	2	0	2	0	2	0	n/a	n/a	2	0	2	0	2	0
T17	0	2	2	0	2	0	0	2	2	0	2	0	2	0	2	0
T18	1	1	2	0	2	0	2	0	2	0	1	1	2	0	1	1
T19	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T20	0	2	2	0	2	0	0	2	2	0	2	0	2	0	2	0
T21	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T22	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T23	1	1	2	0	2	0	1	1	2	0	1	1	0	2	2	0
T24	0	2	1	1	2	0	0	2	2	0	2	0	2	0	2	0
T25	0	2	2	0	2	0	2	0	2	0	2	0	2	0	0	2
T26	1	1	2	0	2	0	1	1	2	0	2	0	2	0	2	0
T27	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
T28	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
T30	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
T31	2	0	2	0	2	0	2	0	2	0	1	1	2	0	1	1
T32	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T33	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T34	0	2	2	0	2	0	1	1	2	0	0	2	0	2	2	0
T35	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T37	0	2	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T38	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T39	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
T40	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T41	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T42	1	1	2	0	2	0	1	1	2	0	2	0	2	0	1	1
T43	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T44	0	2	2	0	2	0	1	1	2	0	1	1	1	1	1	1
T45	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T46	0	2	2	0	2	0	1	1	2	0	2	0	2	0	2	0
T47	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T48	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0

FIGURE 8b, sheet 3 of 12

	Intron 6 423232		Intron 6 423258		Intron 7 460553		Intron 7 460564		exon 8 461199		exon 8 461199		exon 8 461231		exon 8 461337	
	C	G	A	G	C	T	G	A	G	A	T	C	A	G	A	C
	0.98	0.02	0.89	0.11	0.96	0.04	0.99	0.01	0.86	0.12	0.99	0.01	0.99	0.01	1.00	0.00
T1	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T2	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T3	2	0	2	0	2	0	2	0	1	1	1	1	2	0	2	0
T4	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T5	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T6	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
T7	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T8	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T9	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T11	2	0	2	0	2	0	2	0	0	2	2	0	2	0	2	0
T12	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
T13	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T14	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
T15	2	0	1	1	2	0	2	0	1	1	n/a	n/a	n/a	n/a	n/a	n/a
T16	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T17	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T18	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
T19	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T20	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T21	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T22	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T23	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
T24	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T25	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T26	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T27	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T28	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T30	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T31	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
T32	2	0	2	0	1	1	2	0	2	0	2	0	1	1	2	0
T33	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T34	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
T35	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T37	2	0	2	0	2	0	1	1	1	1	2	0	2	0	2	0
T38	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T39	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T40	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T41	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T42	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T43	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0
T44	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0
T45	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T46	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
T47	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T48	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0

FIGURE 8b, sheet 4 of 12

	exon 8 461520		exon 8 461843		exon 8 461968		exon 8 462125		exon 8 4623998		exon 8 462683		exon 8 462949		exon 8 463958	
	C	G	G	A	T	C	C	T	G	A	C	A	T	G	T	C
	0.97	0.03	0.99	0.01	0.51	0.49	1.00	0.00	1.00	0.00	0.95	0.05	1.00	0.00	0.96	0.04
T1	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T2	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T3	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T4	2	0	2	0	0	2	n/a	n/a	2	0	2	0	2	0	1	1
T5	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T6	2	0	2	0	1	1	2	0	2	0	1	1	2	0	2	0
T7	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T8	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T9	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T11	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T12	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T13	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
T14	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T15	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T16	2	0	2	0	2	0	2	0	2	0	1	1	2	0	n/a	n/a
T17	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T18	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T19	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1
T20	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T21	2	0	2	0	n/a	n/a	2	0	2	0	2	0	2	0	2	0
T22	2	0	2	0	1	1	2	0	n/a	n/a	2	0	2	0	1	1
T23	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T24	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T25	2	0	2	0	2	0	2	0	2	0	0	2	2	0	2	0
T26	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
T27	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T28	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T30	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T31	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T32	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T33	1	1	2	0	1	1	2	0	2	0	2	0	2	0	n/a	n/a
T34	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T35	2	0	1	1	0	2	2	0	2	0	2	0	2	0	n/a	n/a
T36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T37	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T38	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T39	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T40	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T41	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T42	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T43	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T44	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T45	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
T46	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
T47	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
T48	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0

FIGURE 8b, sheet 5 of 12

	exon 8 463966		exon 8 464237		exon 8 464735		exon 8 465074		exon 8 54404		exon 8 54460	
	C	T	G	A	T	A	T	C	G	A	C	A
	0.99	0.01	0.98	0.02	0.96	0.04	1.00	0.00	0.74	0.26	0.97	0.03
T1	2	0	2	0	2	0	2	0	2	0	2	0
T2	2	0	2	0	2	0	2	0	2	0	2	0
T3	2	0	2	0	2	0	2	0	2	0	2	0
T4	2	0	2	0	1	1	2	0	2	0	2	0
T5	2	0	2	0	2	0	2	0	2	0	2	0
T6	2	0	2	0	1	1	2	0	2	0	1	1
T7	2	0	2	0	2	0	2	0	1	1	2	0
T8	2	0	1	1	2	0	2	0	2	0	2	0
T9	2	0	2	0	2	0	2	0	2	0	2	0
T10	2	0	2	0	2	0	2	0	1	1	2	0
T11	2	0	2	0	2	0	2	0	2	0	2	0
T12	2	0	2	0	2	0	2	0	0	2	2	0
T13	2	0	2	0	2	0	2	0	1	1	2	0
T14	2	0	2	0	2	0	2	0	2	0	2	0
T15	2	0	2	0	2	0	2	0	2	0	2	0
T16	n/a	n/a	2	0	1	1	2	0	1	1	1	1
T17	2	0	2	0	2	0	2	0	2	0	2	0
T18	2	0	2	0	2	0	2	0	2	0	2	0
T19	2	0	2	0	2	0	2	0	2	0	2	0
T20	2	0	2	0	2	0	2	0	2	0	2	0
T21	2	0	2	0	2	0	2	0	1	1	n/a	n/a
T22	2	0	2	0	1	1	2	0	2	0	2	0
T23	2	0	2	0	2	0	2	0	1	1	2	0
T24	2	0	2	0	2	0	2	0	2	0	2	0
T25	2	0	2	0	2	0	2	0	1	1	2	0
T26	2	0	2	0	2	0	2	0	1	1	2	0
T27	2	0	2	0	2	0	2	0	2	0	n/a	n/a
T28	2	0	2	0	2	0	2	0	0	2	2	0
T29	2	0	2	0	2	0	2	0	2	0	2	0
T30	2	0	2	0	2	0	2	0	2	0	2	0
T31	2	0	2	0	2	0	2	0	1	1	2	0
T32	2	0	2	0	2	0	2	0	1	1	n/a	n/a
T33	n/a	n/a	2	0	2	0	2	0	1	1	2	0
T34	1	1	2	0	2	0	2	0	1	1	2	0
T35	n/a	n/a	2	0	2	0	2	0	2	0	n/a	n/a
T36	2	0	2	0	2	0	2	0	0	2	2	0
T37	2	0	2	0	2	0	2	0	2	0	2	0
T38	2	0	2	0	2	0	2	0	2	0	2	0
T39	2	0	2	0	2	0	2	0	1	1	2	0
T40	2	0	2	0	2	0	2	0	1	1	2	0
T41	2	0	2	0	2	0	2	0	n/a	n/a	n/a	n/a
T42	2	0	2	0	2	0	2	0	0	2	2	0
T43	2	0	2	0	2	0	2	0	n/a	n/a	n/a	n/a
T44	2	0	2	0	2	0	2	0	n/a	n/a	n/a	n/a
T45	2	0	1	1	2	0	2	0	2	0	n/a	n/a
T46	2	0	2	0	2	0	2	0	2	0	n/a	n/a
T47	2	0	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a
T48	2	0	2	0	2	0	2	0	1	1	2	0

FIGURE 8b, sheet 6 of 12

	exon 1A 170035		exon 1A 170068		exon 1A 170256		exon 1A 170368		exon 1A 170487		exon 1B 169812		exon 1B 169823		exon 1C 167950	
	C	A	G	T	C	T	A	G	G	C	C	G	A	G	C	G
sum tumor	92	0	93	1	52	42	95	1	82	12	95	1	95	1	94	2
blood freq	1.00	0.00	0.99	0.01	0.50	0.50	0.99	0.01	0.92	0.08	0.99	0.01	0.99	0.01	0.98	0.02
B1	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B2	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B3	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B4	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B5	B6	B7	B8	0	2	0	2	0	2	0	2	0	2	0	2	0
B6	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B7	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B8	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B9	n/a	n/a	n/a	n/a	1	1	2	0	n/a	n/a	2	0	2	0	2	0
B10	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B11	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B12	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B13	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B14	2	0	2	0	1	1	2	0	2	0	1	1	1	1	2	0
B15	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B16	n/a	n/a	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0	2	0
B17	2	0	1	1	1	1	2	0	2	0	2	0	2	0	2	0
B18	2	0	2	0	2	0	2	0	1	1	2	0	2	0	1	1
B19	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B20	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B21	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B22	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B23	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B24	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B25	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B26	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B27	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B28	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B30	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B31	2	0	2	0	2	0	1	1	0	2	2	0	2	0	1	1
B32	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B33	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B34	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B35	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B37	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B38	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B39	n/a	n/a	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B40	2	0	2	0	0	2	2	0	1	1	2	0	2	0	2	0
B41	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B42	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B43	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B44	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B45	2	0	2	0	2	0	2	0	0	2	2	0	2	0	2	0
B46	n/a	n/a	n/a	n/a	na	na	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B47	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B48	n/a	n/a	2	0	0	2	2	0	2	0	2	0	2	0	2	0

FIGURE 8b, sheet 7 of 12

	exon 1C 167989		exon 1C 168054		exon 1E 64331		exon 1F 52901		exon 1F 52877		exon 1G 18783		exon 1G 18937		exon 1G 19034	
	T	G	C	G	C	T	C	T	G	T	C	T	A	C	T	C
sum tumor	80	16	95	1	60	36	78	0	78	0	96	0	96	0	96	0
blood freq	0.84	0.16	0.99	0.01	0.64	0.36	1.00	0.00	0.97	0.03	1.00	0.00	1.00	0.00	0.99	0.01
B1	2	0	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B2	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B3	2	0	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B4	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B5	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B6	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B7	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B8	0	2	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B9	2	0	2	0	0	2	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B11	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B12	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B13	2	0	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B14	1	1	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B15	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B16	2	0	2	0	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B17	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B18	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B19	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B20	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B21	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B22	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B23	2	0	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B24	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
B25	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B26	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B27	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B28	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B29	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B30	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B31	0	2	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B32	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B33	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B34	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B35	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
B36	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B37	1	1	1	1	1	1	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B38	1	1	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B39	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B40	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B41	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B42	1	1	2	0	0	2	2	0	2	0	2	0	2	0	1	1
B43	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B44	2	0	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0
B45	0	2	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B46	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B47	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B48	2	0	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0

FIGURE 8b, sheet 8 of 12

	Intron 3 243187		exon 3 243055		exon 4 306292		exon 4 306382		exon 6 423067		Intron 6 423149		Intron 6 423163		Intron 6 423220	
	C	T	C	T	G	A	C	G	T	C	G	T	A	G	G	A
sum tumor	60	36	93	3	93	1	78	16	94	0	84	12	86	10	67	29
blood freq	0.59	0.41	0.98	0.02	0.99	0.01	0.82	0.18	1.00	0.00	0.89	0.11	0.90	0.10	0.70	0.30
B1	1	1	2	0	2	0	1	1	2	0	2	0	2	0	2	0
B2	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B3	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B4	1	1	1	1	2	0	1	1	2	0	2	0	2	0	1	1
B5	1	1	2	0	2	0	1	1	2	0	2	0	2	0	1	1
B6	1	1	2	0	1	1	1	1	2	0	1	1	1	1	2	0
B7	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B8	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B9	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B11	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B12	1	1	2	0	2	0	1	1	2	0	1	1	1	1	2	0
B13	0	2	2	0	2	0	2	0	2	0	2	0	1	1	1	1
B14	0	2	2	0	2	0	2	0	2	0	0	2	1	1	2	0
B15	1	1	2	0	2	0	2	0	2	0	1	1	1	1	2	0
B16	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B17	0	2	2	0	2	0	0	2	2	0	2	0	2	0	2	0
B18	1	1	2	0	2	0	2	0	2	0	1	1	2	0	1	1
B19	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B20	0	2	2	0	2	0	0	2	2	0	2	0	2	0	2	0
B21	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B22	2	0	2	0	2	0	1	1	2	0	2	0	2	0	2	0
B23	1	1	2	0	2	0	1	1	2	0	1	1	0	2	2	0
B24	0	2	1	1	2	0	0	2	2	0	2	0	2	0	2	0
B25	0	2	2	0	2	0	2	0	2	0	2	0	2	0	0	2
B26	1	1	2	0	2	0	1	1	2	0	2	0	2	0	2	0
B27	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
B28	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
B30	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B31	2	0	2	0	2	0	2	0	2	0	1	1	2	0	1	1
B32	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B33	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B34	0	2	2	0	2	0	1	1	2	0	0	2	0	2	2	0
B35	0	2	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B37	0	2	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B38	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B39	2	0	2	0	2	0	2	0	2	0	2	0	2	0	0	2
B40	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B41	1	1	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B42	1	1	2	0	2	0	2	0	2	0	2	0	2	0	0	2
B43	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B44	0	2	2	0	2	0	1	1	2	0	1	1	1	1	1	1
B45	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B46	0	2	2	0	2	0	1	1	2	0	2	0	2	0	2	0
B47	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B48	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0

FIGURE 8b, sheet 9 of 12

	Intron 6 423232		Intron 6 423258		Intron 7 460553		Intron 7 460564		exon 8 461199		exon 8 461199		exon 8 461231		exon 8 461337	
	C	G	A	G	C	T	G	A	G	A	T	C	A	G	A	C
sum tumor	94	2	85	11	88	4	91	1	83	13	93	1	93	1	94	0
blood freq	0.98	0.02	0.88	0.13	0.98	0.02	1.00	0.00	#REF!	0.19	0.99	0.01	0.99	0.01	1.00	0.00
B1	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B2	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B3	2	0	2	0	2	0	2	0	1	1	1	1	2	0	2	0
B4	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B5	2	0	2	0	1	1	2	0	1	1	2	0	2	0	2	0
B6	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
B7	1	1	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B8	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B9	2	0	2	0	n/a	n/a	n/a	n/a	1	1	2	0	2	0	2	0
B10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B11	2	0	2	0	2	0	2	0	0	2	2	0	2	0	2	0
B12	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
B13	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
B14	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
B15	2	0	1	1	2	0	2	0	1	1	2	0	2	0	2	0
B16	2	0	2	0	n/a	n/a	n/a	n/a	2	0	n/a	n/a	n/a	n/a	n/a	n/a
B17	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B18	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
B19	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B20	1	1	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B21	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B22	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B23	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
B24	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B25	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B26	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B27	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B28	2	0	2	0	n/a	n/a	n/a	n/a	2	0	2	0	2	0	2	0
B29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B30	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B31	2	0	1	1	2	0	2	0	2	0	2	0	2	0	2	0
B32	2	0	2	0	1	1	2	0	2	0	2	0	1	1	2	0
B33	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B34	2	0	0	2	2	0	2	0	2	0	2	0	2	0	2	0
B35	2	0	2	0	n/a	n/a	n/a	n/a	0	2	2	0	2	0	2	0
B36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B37	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B38	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B39	2	0	2	0	n/a	n/a	n/a	n/a	2	0	n/a	n/a	2	0	2	0
B40	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B41	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B42	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B43	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B44	2	0	1	1	2	0	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a
B45	2	0	2	0	2	0	2	0	1	1	2	0	2	0	2	0
B46	2	0	2	0	n/a	n/a	n/a	n/a	1	1	2	0	2	0	2	0
B47	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B48	2	0	2	0	n/a	n/a	n/a	n/a	2	0	n/a	n/a	n/a	n/a	n/a	n/a

FIGURE 8b, sheet 10 of 12

	exon 8 461520		exon 8 461843		exon 8 461968		exon 8 462125		exon 8 4623998		exon 8 462683		exon 8 462949		exon 8 463958	
	C	G	G	A	T	C	C	T	G	A	C	A	T	G	T	C
sum tumor	93	3	95	1	48	46	94	0	94	0	91	5	96	0	86	4
blood freq	0.97	0.03	0.99	0.01	0.52	0.48	1.00	0.00	1.00	0.00	0.97	0.03	1.00	0.00	0.94	0.06
B1	1	1	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B2	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B3	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B4	2	0	2	0	0	2	2	0	2	0	2	0	2	0	1	1
B5	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B6	2	0	2	0	1	1	2	0	n/a	n/a	2	0	n/a	n/a	2	0
B7	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B8	2	0	2	0	2	0	2	0	n/a	n/a	2	0	2	0	2	0
B9	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B10	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B11	2	0	2	0	0	2	2	0	2	0	2	0	2	0	n/a	n/a
B12	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B13	2	0	2	0	2	0	2	0	n/a	n/a	2	0	2	0	n/a	n/a
B14	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B15	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B16	n/a	n/a	n/a	n/a	n/a	n/a	2	0	2	0	1	1	2	0	n/a	n/a
B17	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B18	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B19	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1
B20	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B21	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B22	2	0	2	0	2	0	2	0	2	0	2	0	2	0	1	1
B23	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B24	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B25	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
B26	2	0	2	0	2	0	2	0	2	0	1	1	2	0	2	0
B27	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B28	2	0	2	0	1	n/a	2	0	2	0	2	0	2	0	n/a	n/a
B29	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B30	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B31	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B32	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B33	1	1	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B34	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B35	2	0	1	1	1	1	2	0	2	0	2	0	2	0	2	0
B36	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B37	2	0	2	0	1	1	2	0	2	0	2	0	n/a	n/a	2	0
B38	2	0	2	0	0	2	2	0	2	0	2	0	2	0	2	0
B39	2	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
B40	2	0	2	0	1	1	2	0	n/a	n/a	2	0	n/a	n/a	n/a	n/a
B41	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B42	2	0	2	0	1	1	2	0	2	0	2	0	2	0	1	1
B43	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B44	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B45	2	0	2	0	1	1	2	0	2	0	2	0	2	0	2	0
B46	2	0	2	0	0	2	2	0	2	0	2	0	2	0	n/a	n/a
B47	2	0	2	0	2	0	2	0	2	0	2	0	2	0	2	0
B48	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

FIGURE 8b, sheet 11 of 12

	exon 8 463966		exon 8 464237		exon 8 464735		exon 8 465074		exon 8 54404		exon 8 54460	
	C	T	G	A	T	A	T	C	G	A	C	A
sum tumor	89	1	94	2	92	4	94	0	65	23	74	2
blood freq	0.99	0.01	0.98	0.02	0.90	0.10	1.00	0.00	0.74	0.26	0.96	0.04
B1	2	0	2	0	2	0	2	0	n/a	n/a	n/a	n/a
B2	2	0	2	0	2	0	2	0	2	0	2	0
B3	2	0	2	0	2	0	2	0	2	0	2	0
B4	2	0	2	0	1	1	2	0	2	0	2	0
B5	2	0	2	0	2	0	2	0	2	0	2	0
B6	2	0	2	0	1	1	2	0	2	0	1	1
B7	2	0	2	0	2	0	2	0	1	1	2	0
B8	2	0	1	1	2	0	2	0	2	0	2	0
B9	2	0	2	0	2	0	2	0	n/a	n/a	n/a	n/a
B10	2	0	2	0	2	0	2	0	1	1	2	0
B11	n/a	n/a	2	0	2	0	2	0	2	0	2	0
B12	2	0	2	0	1	1	2	0	1	1	2	0
B13	n/a	n/a	2	0	1	1	2	0	n/a	n/a	n/a	n/a
B14	2	0	2	0	2	0	2	0	2	0	n/a	n/a
B15	2	0	2	0	2	0	2	0	2	0	2	0
B16	n/a	n/a	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a
B17	2	0	2	0	2	0	2	0	2	0	2	0
B18	2	0	2	0	2	0	2	0	1	1	2	0
B19	2	0	2	0	1	1	2	0	2	0	2	0
B20	2	0	2	0	2	0	2	0	2	0	2	0
B21	2	0	2	0	2	0	2	0	1	1	2	0
B22	2	0	2	0	1	1	2	0	2	0	2	0
B23	2	0	2	0	2	0	2	0	1	1	2	0
B24	2	0	2	0	2	0	2	0	2	0	2	0
B25	2	0	2	0	1	1	2	0	1	1	1	1
B26	2	0	2	0	1	1	2	0	1	1	1	1
B27	2	0	2	0	2	0	2	0	1	1	2	0
B28	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
B29	2	0	2	0	2	0	2	0	0	2	2	0
B30	2	0	2	0	2	0	2	0	2	0	2	0
B31	2	0	2	0	2	0	2	0	1	1	2	0
B32	2	0	2	0	2	0	2	0	2	0	2	0
B33	2	0	2	0	2	0	2	0	1	1	2	0
B34	1	1	2	0	2	0	2	0	1	1	2	0
B35	2	0	2	0	2	0	2	0	1	1	2	0
B36	2	0	2	0	2	0	2	0	0	2	2	0
B37	2	0	2	0	2	0	2	0	2	0	2	0
B38	2	0	2	0	2	0	2	0	2	0	2	0
B39	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
B40	2	0	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a
B41	2	0	2	0	2	0	2	0	1	1	2	0
B42	2	0	2	0	1	1	2	0	2	0	2	0
B43	2	0	2	0	2	0	2	0	2	0	2	0
B44	2	0	2	0	2	0	2	0	1	1	2	0
B45	2	0	1	1	2	0	2	0	2	0	2	0
B46	n/a	n/a	2	0	2	0	n/a	n/a	n/a	n/a	n/a	n/a
B47	2	0	2	0	2	0	2	0	1	1	2	0
B48	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

FIGURE 8b, sheet 12 of 12

ER 1 Exons with SNPs v2.0

ER1 Exon 1G (18941-19032 *of* SEQ ID NO:1)

```
TTGCTACCTGCTACACCACATTTTCACTAGTATGTGATGTATTCATCACAAACAACAGTATTGGCCAACA
TTTTCCCTCACTGTGAAGTGCACATTTGACATCCTTTAGAAAAATTACTGACGGTTTTGAGACGATTGTT
CTGTGCTTTCTTTCAGTCAGCATAATTTTCCCGAAAGCAGAGATGACTCTTCCAGACTTGCTACCAATGC
TTGAACAAACTGTGTAAGCTTAGTCCAAAAAAAATATTTGATTAATAGATTTTATTTTGGTAGATTCTAA
GGTTCCAAGCagtcagagaaataatcgcagagcctcaaatatctccaaaatctgataccaatccttttga
ttgtgaattatattctgtagctaccaaagaagGTAAGTTTTTATTTTTTCTACTCTATTAACTTTCCCTT
GGACAACTGAATATTAAGATGACTATGTAAGGAGGTTATCAGACCAAGGCCTCACACATCAGGATAAAAG
CACATGCCATAGAAAGAACATTTGTGTCTCAAAAGGTGATACCAAGACAAGGCTGTGGGATATATATGGG
```

Exon ER1 1F (52818-52940 of SEQ ID NO:1)

```
TTCCAACTCCACATGCCTGTCTAGACTTCAAGCTTTATTACGAATAAAGAGAAAATCGGCTGGATGGCAT
AAAAAATATTTCAGGCAGATTAACACATGATTTACCTCTTCTTGAACATCCATCTTAATGGAAGTGCTAA
GAAAGTTAGATTCGGGCCTGGCTTGGCAAAAGCAAGGCCACCCCCTCCTCTATTTTTTCAATGAGATTTT
CCAATCCTAGTCAAATGGTGGTGCTAGTTCTTTATTTTGAGTTACTGCATTTCCTAATTTCATGGTCAT
AACAGCCTCCTGTCTACCGACTCAGAACGGATTTTACCaaaactgaaaatgcaggctccatgctcagaag
ctctttaacaggctcgaaaggtccatgCtcctttctcctgcccattctatagcataagaagacagtctct   52877 C/A 2,3(N);
gagtgataatcttctcttcaaGTAGGTACTCCTATTTCTTCTCAATTTATTTTTTCCTTTTTGATATAAT
GTGCTACTGTTTACAAGCATATTGTAACTTCAGAGCTTACCTCTCATCTTTAAAAAATGTTCATTTTTTT
GTCTTTCTGCTCCAAGGATATTTTGC
```

Exon ER1 1E (64150-64280 of SEQ ID NO:1)

```
AGCCAAACATTGATTCTTCAGTGCCTATTGATAAGTGAGACTACTTTTCTTTTTAACAGCCTTATTTCAC
TTAAGTGGGGAGTCAAACTAGCTTTAATTAAGGAAATCTGTAGAAATCACCCACATCTCCCTTTCCTTCT
CTGTTAAAAAAACAAAAGgaagaagaaaactaggaaggagtaagcacaaagatctcttcacattctccgg
gactgcggtaccaaatatcagcacagcacttcttgaaaaaggatgtagatttaatctgaactttgaacc
atcactgagGTATGTGTGAACATACTAGTTTCCTCTTTCTCTCTCCTGACTTTGTCCGTAAATTGATAAG   56346 A/G 2,3(N,I,A,S)
ATCTAATTTGGTCATCAGTTTGGAGAACGATTTTTCATTTAATTTCTTTCATTATCAAGTGTGTATTGTC
AGGGGCTTAGCAGTACACCTACTATCTGATGGGCACTCTACATGCGTTGCTT
```

Exon ER1 1D (166228-166322 of SEQ ID NO:1)

```
ATGGGTCTCAAAGGGAGTGGCCGAAATGCAATGGAAAAAGAGAGATTGTAAAGCTAGAAGGCTTAGGAAT
TGCCTCTTGATTAGGTGTGGAAGGCAAGGGAAAATCAGCCCTCGAAGAAGACAGTGAGATTTTAATCTGG
GTGGCTGGAGAGACAGTGATGCTGGGCACAGACACGGGGAAGTTGAGAGGAACACCATGTTTGAGAATGG
```

FIGURE 9, sheet 1 of 7

```
TGACTCATATTTGAACAAGCCtgcaatgcccagcagaccgctggaaaagtggggctggagacacattcaa
cggaggagccagatcaatctttacccttcttcacctgagagagccaGTAAGTCACGGCTGGAACGTGTGT
GTCCAGCAGGAGAGGGTAGGGAGGGAAGCCAAGAGAGCTGGGAGCCCAAGAGTGAAGTTTTTGCCAAAGG
CAGAAGAGGAAAGTCGGCGTAGCACAGTATACTTTCCCACCCATGCTCACCAAGCCCAGGGACAAGGCTC

Exon ER1 1C (168002-168120 of SEQ ID NO:1)
TTTCCAGCCTCCAAGGGTAGGGGCAAAGGGGCTGGGGTTTCTCCTCCCCAGTACAGCTTTCTCTGGCTGT
GCCACACTGCTCCCTGTGAGCAGACAGCAAGTCTCCCCTCACTCCCCACTGCCATTCATCCAGCGCTGTG
CAGTAGCCCAGCTGCGTGTCTGCCGGGAGGGGCTGCCAAGTGCCCTGCCTACTGGCTGCTTCCCGAATCC 167950 C/G 2
CTGCCATTCCACGCACAAACACATCCACACACTCTCTCTGCCTAGttcacacactgagccactcgcacat 167989 T/G 2, 3(all)
gcgagcacattccttccttccttctcaCtctctcggcccttgacttctacaagcccatggaacatttctg 168054 C/G 2
gaaagacgttcttgatccagcaggGTAGGCTTGTTTTGATTTCTCTCTCTGTAGCTTTAGCATTTTGAGA
AAGCAACTTACCTTTCTGGCTAGTGTCTGTATCCTAGCAGGGAGATGAGGATTGCTGTTCTCCATGGGGG

ER1 Exon 1B (169543-169825 of SEQ ID NO:1 of assembled BAC-flanked by red primers)
ER1 Exon 1A (169867-170678 of SEQ ID NO:1 of assembled BAC-flanked by black primers)

TGTGGCTGGCTGCGTATGCAACCGCACACCCCATTCTATCTGCCCTATCTCGGTTACAGTGTAGTCCTCC
CCAGGGTCATCCTATGTACACACTACGTATTTCTAGCCAACGAGGAGGGGGAATCAAACAGAAAGAGAGA
CAAACAGAGATATATCGGAGTCTGGCACGGGGCACATaaggcagcacattagagaaagccggcccctgga
tccgtctttcgcgtttattttaagcccagtcttccctgggccacctttagcagatcctcgtgcgcccccg
ccccctggccgtgaaactcagcctctatccagcagCgacgacaagtAaaGTAAAGTTCAGGGAAGCTGCT 169812 C/G 2, 3(A,S); 169823 A/G 2
CTTTGGGATCGCTCCAAATCgagttgtgcctggagtgatgtttaagccaatgtcagggcaaggcaacagt
ccctggccgtcctccagcacctttgtaatgcatatgagctcgggagaccagtacttaaagttggaggccc
gggagcccaggagctggcggagggcgttcgtcctgggagctgcacttgctccgtcgggtcgcccggcttc
accggacccgcagGctcccggggcagggccggggccagagctcgcgtgtcggcgggacatgcgctgcgtc 170068 G/T 2
gcctctaacctcgggctgtgctctttttccaggtggcccgccggtttctgagccttctgccctgcgggga
cacggtctgcaccctgcccgcggccacggaccatgaccatgaccctccacaccaaagcatcCgggatggc 170256 T/C 2,3(all),6
cctactgcatcagatccaagggaacgagctggagcccctgaaccgtccgcagctcaagatcccccctggag
cggcccctgggcgaggtgtacctggacagcagcAagcccgccgtgtacaactaccccgagggcgccgcct 170368 A/G 2,3(A)
acgagttcaacgccgcggccgccgccaacgcgcaggtctacggtcagaccggcctcccctacggccccgg
gtctgaggctgcGgcgttcggctccaacggcctgggggggtttccccccactcaacagcgtgtctccgagc 170487 g/c 2,3(n,c,a),6
ccgctgatgctactgcacccgccgccgcagctgtcgcctttcctgcagccccacggccagcaggtgccct
actacctggagaacgagcccagcggctacacggtgcgcgaggccggcccgccggcattctacagGTACCC
GCGCCCGCGCCGCCCGTCGGGGTGGCCGCCGCGCCCGGCAGGAGGGAGGGAGGGAGGGAGGGAGAAGGGA
GAGCCTAGGGAGCTGCGGGAGCCGCGGGACGCGCGACCCGAGGGTGCGCGCAGGGAGCCCGGGGCGCGCG
GCCCAGCCCGGGGGTTCTGCGTGCAGCCCGCGCTGCGTTCAGAGTCAAGTTCTCTCGCCGGGCAGCTGAA
AAAAACGTACTCTCCACCCACTTACCGTCCGTGCGAGAGGCAGACCCGAAAGCCCGGGCTTCCTAACAAA
```

FIGURE 9, sheet 2 of 7

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ER1 Exon 2 (204912-205102 of SEQ ID NO:1)

CAAGTTTGCAATAAACAATTTCCCCTCAAGGTTAATATAATAGGCAACACCTTTTGCTGCAACAGACGGC
AAGAGGTAATGAAAGATTAGCTTACATTATGATTCATTATTTCAAAATGTCAGGATAAAGTGGATCTGCT
GCATCTCCCAGAGAGTGCATGTTTTGCTTTTCTAATGTTAATGGATTTACTGTTTTTTCCCCCCAGgcc
aaattcagataatcgacgccagggtggcagagaaagattggccagtaccaatgacaagggaagtatggct
atggaatctgccaaggagactcgctactgtgcagtgtgcaatgactatgcttcaggctaccattatggag
tctggtcctgtgagggctgcaaggccttcttcaagagaagtattcaagGTAATAGTGTGTTGAAAACGAC
TTCTATTTTTGATCCTATGAGCAGATCCTAAGAGCCAAAGCGACTGAGGAAGGAAGACATAGAATCAGCC
ATTTGTACAAAACATGAATCCCTAGTAGGTCCACTAGTATCTTTGGTAGAAACATGGAGAAGAGACAGGA
TCTCAGGAGAAGGAGTTGACACATGGCAGGGCAGCTGAGGCTGAGTAATTCCGCTTCCTTCCTTTGGCAA
GACTCAATCAGTCTTGAGCAACTCTACAGAAGAATTCCACTAGCTGGATCTCTGAGGAAAAAAGAAATGT

ER1 Exon 3 (242970-243086 of SEQ ID NO:1)

ACACCACCATACCCAGGTTTTTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTTGGTCAGGCTGGT
CTTGAACTCCTGACGTCGTGATCCACCTGCCTCGGCCTCCCAAAGTTCTGGGATTACAGGCATGAGCCAC
CGTGCCCGGCCCATGAGAGGTTTTGTTTGCACTTCAAGAAGGACAGAAAAAGGCAGGCAGGCTGGGGAGC
AACATAGTAAGGCTGAGGAAGTGATAGGAAAACAGCCTCCAAAAGGTTTCCCTGTAGATTCTGACTGGCT
AAGTTTCCTGAAATAATATTAATTCTGTCCTCTTGCTTTTAATAGgacataacgactatatgtgtccagc
caccaaccagtgcaccattgataaaaacaggaggaagagctgccaggcctgccggctccgTaaatgctac 243055 C/T 2,6
gaagtgggaatgatgaaaggtgGTAGGTACATCTCTCCCAGGGGCCCTTGGGGATGGCCCTGGCCACCGC
CCAGTGCTGGCTCTACCCATTGGAATAACACCATGGGAATTTTGTGTTTTTTTCTTTTAATTGTTTTTTT 243187 T/C 2,3(all)
TCTATTCTTATTTTTCTTTGCAACAAAAGTATTTTCATAATCCATTTTATTTTAAAAAGGTGGAAGTGTC
TGGAACTGGAA

ER1 Exon 4 (306168-306503 of SEQ ID NO:1)

TATAACACCTGTTACACACACACCCCTACCTAGTGTGTCGGAATCAGTTTGTATGGGCTCACCAAAGCCT
ACTGTTCAATTTTCAGGAGTTTTGTAAGCCATTTGATGTCAGACAAGTGGCCTGAAGTTTGTTATGGTGG
TGGTATTTACACCATGAAAATTGGCATGTTATGGTGGTAGTATTTACACCATGAAAACTGCTACAAATAG
AAATCTTTTTCTTCTTCTCTTGGAGAGCCACTTGTTGAACACTTACCAGCTCACCTGTGCTTGAAAGTAT
TTCTTCAAATAAAATGAAAGCTGGTTAGCTTTGAAAATTTTTTGTATAAAAGTTTACACGGGAAAAAAAT
AAACTAATTTTTTTTTTCCACCTGTGTTTTCAGggatacgaaaagaccgaagaggagggagaatgttgaa
acacaagcgccagagagatgatggggagggcaggggtgaagtggggtctgctggagacatgagagctgcc
aacctttggccaagcccGctcatgatcaaacgctctaagaagaacagcctggccttgtccctgacggccg 306292 G/A 2
accagatggtcagtgccttgttggatgctgagcccccCatactctattccgagtatgatcctaccagacc 306382 C/G 2,3(C,I,S),6
cttcagtgaagcttcgatgatgggcttactgaccaacctggcagacagggagctggttcacatgatcaac
```

FIGURE 9, sheet 3 of 7

tgggcgaagagggtgccagGTAAGAATGCGAAGCGCAGCTTTTAAGAGTCAATAGCTTTTCAAGAACTTG
TTGTGATGTCATGGGAGAAATAGTGGGGGAAAAAGAAGCAATAACATGTTATGTAATTGGTTTCAAGGTT
ACAGGAGATGTGTTCATTTTCAGTATCAATACACTGTAATTTTCCAGGAGATTAGGAAATAATATTTTTA
AATCAGAATCTAGAAGACTGAAATTCTTAAATTGACATAATTTATTTTTAACCCATCTCATTTACCAAAA
AGATTTAGGGTGGACACTACATGGTAAAACTATTTAATAGTGTATGTTCACAGTAGCAGAAACTTTTAAC
ACTAAATGAACTACAAAAGTTTGTAATATTAATGACCTTTGTTGAAAACATCTCAATTATTAATCAAACG

ER1 Exon 5 (373640-373778 of SEQ ID NO:1)

GTAATGATTGGAGAAAGCTTTAATCTCCTAGTTCACCATTAGAAAACAAGAACACATTTTGGTGGTTATT
ACCCGAAGTAATCATAATGTCACCTTTTTTTCCATCTGACTCATTATCCCAAGTGATTTATTTATATATG
GAGTTTTCTGAGTCTTTCTTTTACATATTACAAAAAAAGAGTGTGATTTAGGGACGAAGCAAAGAAATAA
AAATTTAGTGACTTTCATTCTGCCTGTGCCCCAATTCCTATTGGGCATAAGGCAAGTAATTTAAATTTCT
TAGCACCTTAGCATCTTCTACTCAAACAGAAATGAGGAACAGTCACAGGTTACTATTATAGCTGTCTAAG
TAGAAGGCACACAAGTTTTCACACTGAGTATAACACTTTATAGAAAGCTAAGTGTGTTGCTCAAGTTGGT
ACATTTCTGTAGATGTGACACTATGGCACTAAGAAACTTAATGCCACATTGAAATTCATTGAGATAGCTA
GACTTTAAAAATAATTACTTGACTTCACTATAAAGTATGTTCGTATTGCATTTACTCCATCTAGTAGAAA
ATAGACCTTGTCAGTTCAAATCCCTGTTGCATTAATTTCACCAGTAATGAGTCTTTTTCATTTGAGTCAG
CAGGGTTTTTCTTGCTTGTTTTCAGgctttgtggatttgaccctccatgatcaggtccaccttctagaat 5 (227106-227244)
gtgcctggctagagatcctgatgattggtctcgtctggcgctccatggagcacccagggaagctactgtt
tgctCCTAACTTGCTCTTGGACAGGTAAGTGACCTGGCTGTAGCTTAGGAGTAGCATGTTCTTTACGATC
ATAGTTCATTCATGAAACTATTTTATTCATCTCTCGGTGAAGCTTCAGAGAACTTTATTAGGTATGTTTA
CTTAACAAAAGAGTGCATTGGGGGTGATGAAGCCTAGTCAAATTCACAGAAAGCTAAGGATAACTTTCTG
CTAGACATTACCTCAGAAGAATTCTATTATTTCTAATACACACACACACACACACACACACACACACTCA
CACTCTCTCTCTCTCTCTCTCTGTCATTATGAATGGTAATTTTCTAACTCCATCTTCAACTTGTATCATA
TAAAAATTATAATAACCTCTCTTTAATTAAAATCTGTTGTTGCTTCTTGTACATCCATACCACAATAGCC
TATTCATTTTCTTCTCCAATTTTCCCATCCGTAAAATGAAGAAATTTGACCAGAGTTCTGAAGGTCACAT
TCAGGTCGACAAATTCATTTTCATGTTCAAATATGTTACCTTCTTTAACATACCATTCTGGGGTTGCCTT
GGAATGTGGGTCCCATTGTTTTTTTTTTTTCAGTCATTGCTTAGAGTCATAGAATTTAGATATTACTCAA
TAGCAGCTGCCACTGATAGAGTCTCCACCCTGCACCAGCTGTGATGCTAAACACTTTACATATATTATCT
CATTTAATCATCACCGGACTCCTAGGAGGCAGGAATGTCATCATCCATGTTTTACCAGAAAGGAAACTAA
ATCTCAGAGACATCCTGCTACTTGCAAAAAGAGGAAAGCTCACTAAATGGTGGAGCCAGAGTTCAAATTC
AAGATCTTTCTGGCTCCGGTATGCTCTGTTACCTCCTGTGCTGGGCACATGGTCTTCCCACTCTCATGTT

ER1 EXON 6 (422964-423097 of SEQ ID NO:1)

ATTGTAGTTGTTCTTGTACTTCAAAAGCACTACAAAACACAACCATCAGGACTTGTTACATTATTTGAAG
GCTATGAGCATCTTCAGCCGAGGCCCTGTTTTTATTCCCAGAACTACCACATTGTTTAGAATATAGTAGC
AGATCAATATACGTGTATTAGATAAATCGTTTACCCAGATCTTGATCATTTTCAATTACCCATAGGTTGA

FIGURE 9, sheet 4 of 7

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AGAACTCCATATTTAACATGGCAGACTTGAGGACTGAACTACCTACCTCTTCTAAGAAGTTGAAATGAGA
ATGTTTTATTGATGGGAAATTATTTTTTTGTTTTGCCTTCTAGAATTCAAATGAATGTTCATATTCCATG
AAGACAATGGCTGATAGTTTTTTGTTAAAGATTTAGAACCAGTGGATTTTTATGAATGTGAACCCTTTCA
TGTCTTGTGGAAGATTTTCTGTTTTTTAATCTTTTTATTTATTTATTTATTTTTGCTATGTTTTCATAGg  6(276430-276563)
aaccagggaaaatgtgtagagggcatggtggagatcttcgacatgctgctggctacatcatctcggttcc
gcatgatgaatctgcagggagaggagtttgtgtgcctcaaatctattattttgcttaattctgGTGAGTT
GATAACACAAGATAACTCAATGCTGGATGAAATGTTTATTTGTAGTTTTCAACCAGATACGATCTACCCA  423149T/G 2,3(N,C,I,A); 423163 A/G 2,3(N,C,I,A)
CTCCAAAGGCATAATGTCATAAATAGAAAGAAACTACTGACACACATTTTAAAATAACCTACCAACATTG  423220 G/A 2,3(N,C,I,A); 423232 C/G 2
CAGATTCCTTATAAAGGTAGAACCATGCTAGCCAAATAGACACATGAAAAATTGTAATTTGGCATTGAAT  423258 A/G 2,3(N,C,I,A)
CAAATGGCCTTTGAGCTAAAATTTTTGTATGCTTTCACAGATAGGATGTTTTTATTCAAATGGTACATGT
ATATAGACATATGTTAGTTGATAGTTATATTATGTCTGAAAATAAGTAGACCAAGTAATTCTGTTAAGAA


ER1 Exon 7 (456354-456537 of SEQ ID NO:1)
GGGTCCAGAGCATCCCCATTGCTAGACTACTGTGCTGAGGAAGGGCACTGGCTCATTGTTACATCCCATG
AACACTCTGGGTCTCCTAGACCTCATCCTCTTTGAGCTTCTCTCTCTCACTCTCTCTCTGCGCATTCAGg
agtgtacacatttctgtccagcaccctgaagtctctggaagagaaggaccatatccaccgagtcctggac
aagatcacagacactttgatccacctgatggccaaggcaggcctgaccctgcagcagcagcaccagcggc
tggcccagctcctcctcatcctctcccacatcaggcacatgagGTGAGGCATCTGTGGGCTTCCTACAGG
AGAGACATAAAGAAAACATGCCCCCAAACCTATGTGACAGCTGGCCGGGAAGGACTGGTGCCTGCATATG
GAGAGTGCACTTGTGACAGTTCCTGGCATAGAATAAGCATAAATGCTATAGGAGGACAGAAGAGAGAGGT
TTTAAATCTGCGAGGGTCACAGGGCAAGTGTCAGAGAAGGCATAGAGGAAGCGATACTTACGCTTGGTTT

ER1 Exon 8 (460701-465237 of SEQ ID NO:1)

TCAAACTAGATAATAGTTGTTCTCCTCCCCACCCCCGCCACCAGTAGTGTGGTGGGGCAGCAGAGTTGTG
GCTAGTGGAGGAGAGCAGAGGAGGAGAGTAGGGAAAGGAGAATGCCATTTGCCTACATTTCCCTCTGCCC  Forward primer - Coriell
ATTTCCCGCTGCCCATTTCCCCCCTTGTTTTCCTGAACGTGAACTGAGCTCTGGGCACTGTTTTAGGCCT  459706 G/C 3(I)
AGCAGGGGACAGGATAAAGCCTGCTTCTCTAGGAATTCGCACTGAGGGTGTGAGTGTGTGCACGTGTGTG  459832 G/A 3(S)
TTTGGAGGCGGGAGAATAAACACAAATAAATAAAAAGGAGAATTTCAGGCAGTGATAAGAGTGCTGAGAA
AAACAGAACGGTGTGAAAGAGGAAGGCTGAGCCTGCAGAGGCTTGAGGCTGCTGCCACTGGGTAGCGGTA  459913 A/G 3(N,I)
GGCCTTTCCGAGGAGGCGGCATTTGAAGACCGGAGGAAGGTTCATCCCAGCAAGTAGGAACAGCAAGTGT  460024 C/G 3(all)
AGGTCCCCTAAGTCTTGGGGGAGCTTAGTTCCTTTAAGGGCAGCACAAAAATCAGTGTGGCTCCGGAGAG  460056 C/T 3(I)
CACATTAGGGGAGAGAGGCAGGAAGAGCTTGGAGACATGGATGGAAGCTGGACCAGTTGGGCCTTGTTGA
ACATGGAAAGGCATTTAGATCGTATTCTGAGTTAAATGGGAAGTGACGTGAGAGATTTAACAATGGAGCG
TCTTGAACTGCTTTACTCATTTAAAATACCCACTCCTGCTTGGCTGAATATCTCATGTTGTCTTTTTAGA
AGCTTTGGCGATCCTATTTGAATGCATTTAGGTCCTATTGGAGGGGAATAGGATCTCATTTGAGGCCACG
GAGGTCCATGGAAGTCACCTGCATAGCAAATACCCTGAAAGTGGCTGCAGGGAGAGTGTGAGGGTGGGAC
CGCCCTGGTAGGAGGTGGAAAATGAAAAACACACGGCCATGAGTTCCAGATTAGGGCTTCTGAAAGCCCT  8.3 f primer
CAGCTTTCCCAGCTCCCATCCTAAAGTGGGTCTTTAAACAGGAAGAAAGAAAGATTGCTAAGTGTCTTTG  460553 T/C 2,3(I); 460564 G/A 2
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FIGURE 9, sheet 5 of 7

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GAGTTCCTCTTCCTTCCCCTTCTAGGGATTTCAGCACTCCTGGGGCTCGGGTTGGCTCTAAAGTAGTCCT
TTCTGTGTCTTCCCACCTACAGtaacaaaggcatggagcatctgtacagcatgaagtgcaagaacgtggt
gcccctctatgacctgctgctggagatgctggacgcccaccgcctacatgcgcccactagccgtggaggg
gcatccgtggaggagacggaccaaagccacttggccactgcgggctctacttcatcgcattccttgcaaa
agtattacatcacgggggaggcagagggtttccctgccacGgtctgagagctccctggctcccacacggt   460929 A/G 1,2,3(all),4,5,6
tcagataatccctgctgcattttaccctcatcatgcaccactttagccaaattctgtctcctgcatacac
tccggcatgcatccaacaccaatggctttctagatgagtggccattcatttgcttgctcagttcttagtg
gcacatcttctgtcttctgttgggaacagccaaagggattccaaggctaaatctttgtaacagctctctt
tccccttgctatgttactaagcgtgaggaTtcccgtagctcttcacagctgaactcagtctAtgggttg   461199 T/C 2  461231 A/G 2
gggctcagataactctgtgcatttaagctacttgtagagacccaggcctggagagtagacatttttgcctc
tgataagcactttttaaatggctctaagAataagccacagcaaagaatttaaagtggctcctttaattgg   461337 A/C 3(A)
tgacttggagaaagctaggtcaagggtttattatagcaccctcttgtattcctatggcaatgcatccttt
tatgaaagtggtacaccttaaagcttttatatgactgtagcagagtatctggtgattgtcaattcattcc
Ccctataggaatacaaggggcacacagggaaggcagatcccctagttggcaagactattttaacttgata   461520 G/C 2
cactgcagattcagatgtgctgaaagctctgcctctggctttccggtcatgggttccagttaattcatgc
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ggacctgttccagtgggcactgtacttggatcttcccggcGtgtgtgtgccttacacaggggtgaactgt   461843 G/A 2
tcactgtggtgatgcatgatgagggtaaatggtagttgaaaggagcaggggccctggtgttgcatttagc
cctggggcatggagctgaacagtacTtgtgcaggattgttgtggctactagagaacaagagggaaagtag   461968 T/C 2,3(all)
ggcagaaactggatacagttctgaggcacagccagacttgctcagggtggccctgccacaggctgcagct   8.25 f primer
acctaggaacattccttgcagaccccgcattgccctttggggggtgccctgggatccctggggtagtccag   462125 C/T 3(A)
ctcttcttcatttcccagcgtggccctggttggaagaagcagctgtcacagctgctgtagacagctgtgt   8.3r primer
tcctacaattggcccagcaccctggggcacgggagaagggtggggaccgttgctgtcactactcaggctg
actggggcctggtcagattacgtatgcccttggtggtttagagataatccaaaatcagggtttggtttgg
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ctgctcgggcttctcttggtatgtcttgtttggaaaagtggatttcattCatttctgattgtccagttaa   462683 C/A 3(I,A,S)
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ggggacaattttatgtatctgtgttaaggatatgtttaagaacataattcttttgttgctgtttgtttaa
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gtttatcagacaattgaatgtagtaattctgttcTggatttaatttgactgggttaacatgcaaaaacca   462949 T/G (A,S)
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tagacaaaATAGCACTAATCCAGATGCCTATTGTTGGatactgaatgacagacaatcttatgtagcaaag   8.17f primer / 8.25r primer
attatgcctgaaaaggaaaattattcagggcagctaattttgcttttaccaaaatatcagtagtaatatt
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```

FIGURE 9, sheet 6 of 7

ggaaggttttacattattcatccaatgtgtttctattcatgttaagatactactacatttgaagtgggca
gagaacatcagatgattgaaatgttcgcccaggggtctccagcaactttggaaatctctttgtattttta
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gaacaacatcagcagtaaagtccatggaatagctagtggtctgtgtttcttttcgccattgcc**T**agcttg 463958 T/C 3(N)
c**C**gtaatgattctataatgccatcatgcagcaattatgagaggctaggtcatccaaagagaagaccctat 463966 C/T 2
caatgtaggttgcaaaatctaacccctaaggaagtgcagtctttgatttgatttccctagtaaccttgca
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ggcttagagtactccttcccctgcatgacactgattacaaatactttcctattcatactttccaattatg 8.18 f primer
agatggactgtgggtactgggagtgatcactaacaccatagtaatgtctaatattcacaggcagatctgc
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ccaactgcatttcctttccaattgaattaaagtgtggcctc**G**ttttagtcatttaaaattgttttctaa 464237 G/A 2 8.17r primer
gtaattgctgcctctattatggcacttcaattttgcactgtcttttgagattcaagaaaaatttctattc
Tttttttgcatccaattgtgcctgaacttttaaaatatgtaaatgctgccatgttccaaacccatcgtc 464735 A/T 2,3(all)
agtgtgtgtgtttagagctgtgcaccctagaaacaacatattgtcccatgagcaggtgcctgagacacag
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CCTCTAAAATCAAAGTGGTTAAACGATCTGTCACACACAGTGAGTCTGAATGCTAAAGCCTCTCCTCACC 54404 A/G 3(N,C,I,A),54460 C/A 2,3(C,I,S)
TCACTCCCTCTGCCCAACACCCCCAGGTGTATCAGGAAGTGTGTGGACACTGTGGTCAGGCAGAACTGGC
CTCAATTCTTGGCTTCACCACTTACAAATTTTATGATCATTGGCAGTTGATTTTTCAGAGTTTCGGCTTC
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TGAGAGTGGTTATTTA**TGAATGAATGAGTGAATGGAAGAATGAG**TGATCTGAAATGATATAATTAGCTTA
AAAACCTCTCCCTCATTCTGAAGGTAAAGCAGGAACAATTGGTCCACCCCCACCCCAGGTTTCCATTTCA
GGACTCCCTTCCCTTTTTGGAGCTACCTGCGTGCTTCCTTTACCCATTTTCTCAGATTTAACTGATGAAT 8.18r primer

(bold = SNP position, underlined = primer sequences, lowercase = exon.)

FIGURE 9, sheet 7 of 7

SEQUENCE LISTING

<110> KALUSH, Francis; CASSEL, Michael J.; HWANG, Stuart Soo-In; WINN-DEEN, Emily S.

<120> Estrogen receptor alpha variants and methods of detection thereof

<130> CL000258PCT

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<151> 2000-02-22

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aagatattgt gatcttgatt tcgattcttt tggatacata tcctgaagtg ggaaggctgg 180
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gatattctgc ttcttctatc atatggcatg acattgatgg acctttagga cattatccta 360
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/62969 A3

(54) Title: ESTROGEN RECEPTOR ALPHA VARIANTS AND METHODS OF DETECTION THEREOF

(57) Abstract: The present invention is based on sequencing genomic DNA from human chromosome 6 and cDNAs to define the genomic structure of estrogen receptor alpha genes and novel polymorphism/haplotypes in the estrogen receptor gene/protein. Such polymorphism/haplotypes can lead to a variety of disorders that are mediated/modulated by a variant estrogen receptor, such as a susceptibility to cancer, osteoporosis, cardiovascular disorder, etc. Based on this sequencing approach, the present invention provides genomic nucleotide sequences, cDNA sequences, amino acid sequences and sequence polymorphism/haplotypes in the ESR-alpha genes, methods of detecting these sequences/polymorphism/haplotypes in a sample, methods of determining a risk of having or developing a disorder mediated by a variant estrogen receptor and methods of screening for compounds used to treat disorders mediated by a variant estrogen receptor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/05358

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C07K14/705 C07K16/28 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, SEQUENCE SEARCH, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MURPHY L C ET AL.: "Estrogen receptor variants and mutations" JOURNAL OF STEROID BIOCHEMISTRY & MOLECULAR BIOLOGY, vol. 62, no. 5-6, 1997, pages 363-372, XP001010877 cited in the application * see especially Table 2 * the whole document ---	17

-/--

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2001	20. 11. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Knehr, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOTZLAW H ET AL.: "Characterization of estrogen receptor variant mRNAs from human breast cancers" MOLECULAR ENDOCRINOLOGY, vol. 6, no. 5, 1992, pages 773-785, XP001012041 * see especially nucleotide position 232 within Fig.2 * the whole document ---	17
A	SCHUBERT E L ET AL.: "Single nucleotide polymorphisms (SNPs) in the estrogen receptor gene and breast cancer susceptibility" JOURNAL OF STEROID BIOCHEMISTRY & MOLECULAR BIOLOGY, vol. 71, November 1999 (1999-11), pages 21-27, XP001010874 * see especially Fig.1 * the whole document ---	
A	LEMIEUX P AND FUQUA S: "The role of the estrogen receptor in tumor progression" THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 56, no. 1-6, 1996, pages 87-91, XP001010876 * see especially page 89, column 2, paragraph 1 * the whole document ---	
A	WILTSCHKE C ET AL.: "Isolation of a 'super-active' estrogen receptor variant from premalignant breast lesions" BREAST CANCER RESEARCH TREATMENT, vol. 37, no. Sup, 1996, page 40 XP001011239 abstract ---	
A	LORENTZON M ET AL.: "Estrogen receptor gene polymorphism, but not estradiol levels, is related to bone density in healthy adolescent boys: A cross-sectional and longitudinal study" THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 84, no. 12, 1999, pages 4597-4601, XP001011802 the whole document --- -/--	

International Application No
PCT/US 01/05358

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JAZAERI O ET AL.: "Expression of estrogen receptor alpha mRNA and protein variants in human endometrial carcinoma" GYNECOLOGIC ONCOLOGY, vol. 74, July 1999 (1999-07), pages 38-47, XP001011870 the whole document ---	
A	GREEN S ET AL.: "Human oestrogen receptor cDNA: sequence, expression and homology to v-erb-A" NATURE, vol. 320, 1986, pages 134-139, XP001009860 cited in the application abstract; figure 2 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/05358

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1-16
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
17 (partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-16

Claims 1-16 refer to peptide variants of an estrogen receptor protein, an antibody selectively binding to such a peptide variant, nucleic acids (or fragments thereof) encoded by such peptide variants, vectors and host cells comprising such encoded nucleic acid sequences, methods for producing or detecting such peptide variants or encoded nucleic acids, kits comprising reagents suitable in such methods, as well as a method for identifying an agent binding to such peptide variants. However, the application does not disclose such peptide variants, neither in Fig.2 (which discloses short nucleic acid fragments of ESR-alpha comprising single nucleotide polymorphisms) nor in Fig. 3 (which discloses the only peptide sequence within the whole application and which represents the wild type sequence of ESR-alpha [first published in 1986]).
Since no variant peptide sequences have been disclosed within the application, a lack of clarity and conciseness within the meaning of Article 6 PCT arises for claims 1-16 rendering a meaningful search for these claims impossible. Consequently, the search has been carried out for those parts of the application which are supported by the description and do appear to be clear and concise, namely claim 17 disclosing SNP gene polymorphisms as shown in Fig.2, as well as patient haplotypes as enlisted in Fig.4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claim : 17 (partially)

   INVENTION 1:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 1A according to Fig.2.

2. Claim : 17 (partially)

   INVENTION 2:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 1B according to Fig.2.

3. Claim : 17 (partially)

   INVENTION 3:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within intron 1D according to Fig.2.

4. Claim : 17 (partially)

   INVENTION 4:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 1C according to Fig.2.

5. Claim : 17 (partially)

   INVENTION 5:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within intron 1E according to Fig.2.

6. Claim : 17 (partially)

   INVENTION 6:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 1F according to Fig.2.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claim : 17 (partially)

   INVENTION 7:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 1G according to Fig.2.

8. Claim : 17 (partially)

   INVENTION 8:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within intron 1G according to Fig.2.

9. Claim : 17 (partially)

   INVENTION 9:
   A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within intron 3 according to Fig.2.

10. Claim : 17 (partially)

    INVENTION 10:
    A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 3 according to Fig.2.

11. Claim : 17 (partially)

    INVENTION 11:
    A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 4 according to Fig.2.

12. Claim : 17 (partially)

    INVENTION 12:
    A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 6 according to Fig.2.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

13. Claim : 17 (partially)

INVENTION 13:
A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within intron 6 according to Fig.2.

14. Claim : 17 (partially)

INVENTION 14:
A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within intron 8 according to Fig.2.

15. Claim : 17 (partially)

INVENTION 15:
A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon a single nucleotide polymorphism within exon 8 according to Fig.2.

16. Claim : 17 (partially)

INVENTION 16:
A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon haplotype #1-6 according to Fig.4a (Liverpool tumors).

17. Claim : 17 (partially)

INVENTION 17 TO INVENTION 117:
A method of identifying an individual having or at risk of developing a disorder mediated by a variant estrogen receptor based upon haplotype #2-7, #3, ..., and #102, according to Fig.4a (Liverpool tumors).

Invention 17 refers to haplotype #2-7,
Invention 18 refers to haplotype #3,
...
Invention 117 refers to haplotype #102.